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**TISSUE BANKS: THE DANGERS OF TAINTED
TISSUES AND THE NEED FOR FEDERAL
REGULATION**

HEARING

BEFORE THE

**COMMITTEE ON
GOVERNMENTAL AFFAIRS
UNITED STATES SENATE
ONE HUNDRED EIGHTH CONGRESS**

FIRST SESSION

MAY 14, 2003

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C O N T E N T S

	Page
Opening statement:	
Senator Collins	1
Senator Coleman	4
Senator Pryor	6
Senator Carper	24
 WITNESSES	
Steve and Leslie Lykins, parents of Brian Lykins, accompanied by daughter Tammy	6
Steven L. Solomon, M.D., Acting Director, Division of Healthcare Quality Promotion, National Center for Infectious Diseases, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services	15
Jeanne V. Linden, M.D., Director, Blood and Tissue Resources, Wadsworth Center, New York State Department of Health	17
Jesse L. Goodman, M.D., Director, Center for Biologics Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services	26
 ALPHABETICAL LIST OF WITNESSES	
Goodman, Jesse L., M.D.:	
Testimony	26
Prepared Statement with an attachment	61
Linden, Jeanne V., M.D.:	
Testimony	17
Prepared Statement with an attachment	55
Lykins, Leslie and Steve:	
Testimony	6
Prepared Statement	39
Solomon, Steven L., M.D.:	
Testimony	15
Prepared Statement	44
 EXHIBITS	
1. Deposition of James C. Vander Wyk, Ph.D., taken on January 21, 2003, on behalf of the plaintiff in the case of <i>Steve Lykins v. CryoLife, Inc.</i> ; Civil Action File Number 02105613-24; Superior Court of Cobb County, State of Georgia; pages 1-4, 25-32, 69-80, and 189-192	84
2. "Update: Allograft-Associated Bacterial Infections—United States, 2002," <i>Mortality and Morbidity Weekly Report</i> ; Centers for Disease Control and Prevention; March 15, 2003, at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5110a2.htm	91
3. "Hepatitis C Virus Transmission from an Antibody-Negative Organ and Tissue Donor—United States, 2000–2002," <i>Mortality and Morbidity Weekly Report</i> ; Centers for Disease Control and Prevention; April 4, 2003, at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5213a2.htm	96
4. Letter from Senator Susan M. Collins, Ranking Minority Member, Permanent Subcommittee on Investigations, to Bernard A. Schatz, D.V.M., Ph.D., Acting Principal Deputy Commissioner, Food and Drug Administration (FDA), December 21, 2001, concerning the death of Brian Lykins and the status of the FDA's tissue action plan	100

IV

Page

5. Letter from Senator Susan M. Collins, Ranking Minority Member, Permanent Subcommittee on Investigations, to Bernard A. Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner, Food and Drug Administration (FDA), February 11, 2002, concerning the status of the FDA's tissue action plan	101
6. Letter from Melinda K. Plaisier, Associate Commissioner for Legislation, Food and Drug Administration (FDA), to Senator Susan M. Collins, Ranking Minority Member, Permanent Subcommittee on Investigations, April 3, 2002, concerning the status of the FDA's tissue action plan	103
7. Letter from Senator Susan M. Collins, Ranking Minority Member, Permanent Subcommittee on Investigations, to The Honorable Tommy G. Thompson, Secretary of Health and Human Services, April 12, 2002, concerning the status of the FDA's tissue action plan	106
8. Letter from The Honorable Tommy G. Thompson, Secretary of Health and Human Services, to Senator Susan M. Collins, Ranking Minority Member, Permanent Subcommittee on Investigations, August 28, 2002, concerning the status of the FDA's tissue action plan	109
9. Responses to questions for the record, transcript of hearing on the nomination of Mark B. McClellan, to be Commissioner of the Food and Drug Administration, Department of Health and Human Services; U.S. Senate Committee on Health, Education, Labor, and Pensions, October 2002	110
10. FDA Notice of Inspectional Observations (Form FDA-483) from Inspection 3/25/2002-4/12/2002 (FEI #3001451326), issued to James C. Vander Wyk, Vice-President of Quality Assurance/Regulatory Affairs, CryoLife Inc., dated April 12, 2002	111
11. Letter from James C. Vander Wyk, Ph.D., Vice-President, Regulatory Affairs and Quality Assurance, CryoLife, Inc., to Mr. Ballard H. Graham, District Director, HFE-SE100, Food and Drug Administration, regarding "Initial reply to Notice of Inspectional Observations (483) from Inspection of 3/25/2002-4/12/2002 (FEI #3001451326), dated May 15, 2002	119
12. Sample of Complaint Record, CryoLife, Inc	121

TISSUE BANKS: THE DANGERS OF TAINTED TISSUES AND THE NEED FOR FEDERAL REGULATION

WEDNESDAY, MAY 14, 2003

**U.S. SENATE,
COMMITTEE ON GOVERNMENTAL AFFAIRS,
*Washington, DC.***

The Committee met, pursuant to notice, at 9:37 a.m., in room SD-342, Dirksen Senate Office Building, Hon. Susan M. Collins, Chairman of the Committee, presiding.

Present: Senators Collins, Coleman, Carper, and Pryor.

OPENING STATEMENT OF CHAIRMAN COLLINS

Chairman COLLINS. The Committee will come to order.

Good morning. Today, the Committee on Governmental Affairs is holding a hearing on the dangers of tainted human tissue and the need for Federal regulation of the tissue bank industry.

Tissue banks procure, process, store, and distribute human tissue for transplantation. Tissue transplants have soared in recent years due to advances in technology that have greatly reduced the risk of rejection. The American Association of Tissue Banks estimates that more than 800,000 tissue products were made available for transplantation last year in the United States. Yet despite the ever increasing number of transplants, there are serious questions about the safety of our Nation's tissue supply.

Some of these concerns stem from the Food and Drug Administration's failure to finalize much-needed regulations governing the tissue bank industry. This is not a new problem. In fact 2 years ago this month I chaired a hearing of the Permanent Subcommittee on Investigations exposing the safety issues concerning the practices of some tissue banks. Yet in the intervening 2 years, the FDA has made virtually no progress in strengthening the regulatory requirements for an industry whose products are in wide use and affect human health.

While many people are familiar with the concept of organ donation, tissue donation is not as well understood. Human tissue, including tendons, bone, and skin is unlike an organ transplant because it is not usually transplanted as-is from the donor's body into that of the recipient.

Rather, donated tissue generally undergoes considerable processing before it is transplanted into a patient. Bone from a donor's femur, for example, may be completely reshaped into a component

designed to give support to a recipient's spine. The reconfigured tissues are also known as allografts.

Once processed, donated tissue can be stored for a period of time before it is used to enhance, improve, and even save lives. If, however, human tissue is not properly processed, it can pose dangerous risks to the recipient.

Therefore, it is critical that the tissue come from carefully screened donors, and that it be properly processed and stored. Otherwise, communicable diseases such as HIV and hepatitis, among others, can be transmitted through the tissue to the recipient.

The FDA has been aware of these public health risks for years. In 1997, the agency examined the health issues involving tissue transplantation and concluded that the existing regulatory framework was insufficient. The agency undertook the review in response to incidents in which imported foreign tissue had tested positive for serious diseases.

The FDA then notified the tissue bank industry that it intended to make regulatory changes to strengthen the oversight of tissue banks. The changes were threefold. First, all tissue banks would be required to register with the FDA. Second, screening of potential donors would be expanded to require testing for the human variant of mad cow disease, syphilis, and other viruses. And third, and perhaps most important, a rule would be issued on the methods and controls used during the processing of human tissue.

This third proposal, known as the good tissue practices rule is intended to help ensure that tissues are not contaminated as they move from recovery to distribution.

The hearing that I held 2 years ago exposed dangerous practices by some tissue banks as well as the inadequacy of the regulatory framework. The testimony that we heard at that time was deeply troubling. First of all, we learned that the Federal Government had no idea how many tissue banks were operating in the country. The Department had estimated that there were about 150, but approximately 350 tissue banks registered with the FDA when the registration requirement went into effect. But that indicated that many tissue banks were operating without any Federal oversight whatsoever.

Second, there was also considerable testimony about the unacceptable practices of some tissue banks. For example, a deputy inspector general from the Department of Health and Human Services testified about unscrupulous tissue banks that engaged in a practice in which tissues that initially tested positive for contamination were simply tested over and over again until the technicians achieved the negative result they wanted.

Another witness testified that a Lion's eye bank, which also participated in tissue recovery, accepted a donor who was 82-years-old and had a history of cancer. That is a frightening example of inadequate donor screening by a tissue bank.

Based on our findings, it was evident to the Subcommittee that Federal oversight of tissue banks was woefully inadequate. Until the necessary changes were made, gaping holes would remain in the safety net that protects patients who receive transplanted tissue. Now the FDA assured us at this hearing 2 years ago that it

would act expeditiously to remedy this problem by implementing the long-overdue regulations.

Since that time, I have repeatedly pressed the FDA to finalize its regulations. I have offered help to the agency to overcome any obstacles that it might face along the way. Senator Durbin and I asked the FDA to provide a breakdown of the costs for implementation of the proposed regulations. We never received a response. I wrote additional letters to the FDA. I then wrote to the Department of Health and Human Services about the very troubling delays and seeking assurance that the implementation of the regulations was a priority. In its response, the Department agreed that the FDA needed to move as quickly as possible to finally put the regulations in effect.

Unfortunately, the FDA still has not kept its commitment to addressing this public health risk through effective regulation. And, as I predicted 2 years ago, the result of this bureaucratic inertia has been tragedy.

My greatest fears were realized when Brian Lykins, a healthy 23-year-old man from Minnesota, died in November 2001 after receiving a tissue transplant in his knee during routine surgery. The tissue was infected with a deadly bacterium, and yet it made its way from Georgia to St. Cloud Hospital in Minnesota.

Good tissue practices appear to have been totally absent in this case. CryoLife, the company that processed the tissue used in Brian's transplant, accepted a tissue donation from an individual who had been deceased for 19 hours and his body had not been refrigerated during that time. I dare say that if Brian had been aware of that fact alone, he would have refused to have a transplant of that donor.

Brian's parents will testify before the Committee today about the devastating loss that their family have suffered. It is a tribute to them and to their daughter Tammy that they have agreed to come forward and testify publicly about this most painful and private event. They have done so in the hope that others will not have to endure the tragic loss that they have suffered.

I just want to thank them publicly for their willingness to speak out and for their commitment to seeing that no other family suffers the tragedy that they have. So I want to thank you for being with us today. My hope is that their participation in today's hearing will finally be the catalyst that prompts the FDA to act.

In the wake of the tragedy of Brian's death, 6 months later in May 2002, an FDA official stated on national television that the agency intended to make the regulations final within 1 year. Yet here we are a full year after that, without any discernible progress having been made toward issuing the regulations. I just do not understand that. That is why I am holding this hearing today.

Moreover, there is now evidence to suggest that the absence of regulations is being used as a legal defense for questionable practices. After Brian Lykins died, his family filed suit against the tissue processor, CryoLife.

In a deposition, a CryoLife executive stated that the FDA had not imposed final regulations regarding what industry practices should be, but instead had issued only non-binding guidance. That CryoLife representative is correct on that point. Under the current

regulations, a tissue bank is not even required to report situations to the FDA in which an adverse event—that is bureaucratic language for what happened to Brian Lykins—has occurred. Reporting is completely voluntary. As outrageous as that may seem, perhaps the industry's defense strategy will provoke the FDA into action.

Recent evidence confirms that Brian Lykins' case was not an isolated event. Last year after his death, an investigation was undertaken by the Centers for Disease Control and Prevention along with the New York and Minnesota State Departments of Health, to determine what killed him. That inquiry led the CDC to examine other cases of allograft-related infections.

In its March 2002 report, the CDC identified 26 cases of infection in donated human tissue that had been linked to allografts used in transplants. The CDC now reports that more than 60 cases of transplanted tissue infections are now being investigated. We will hear more about that from the CDC today.

It is also surely significant that New York State, which has the most stringent tissue oversight regulations in the country, had not experienced the same problems. Today we will hear testimony from that State's top tissue oversight official regarding the authority that has allowed New York State residents to have greater confidence that the tissue transplants they received are free from infection.

It is well past time for the FDA to finish what it started more than 6 years ago when the agency correctly identified a serious threat to public health and the need to improve regulatory oversight of the tissue industry. The remaining safety regulations must be completed without delay, and tissue banks that do not comply with the regulations must be suspended from doing business and punished for jeopardizing public health.

Last year, Senator Durbin and I introduced a bill, the Tissue Transplant Safety Act of 2002. It would have required the FDA to impose tougher safety standards. Later today, Senator Durbin, Senator Coleman, and I will reintroduce that legislation which we, with the family's permission, are naming in honor of Brian Lykins. This time we will require the FDA to issue the final regulations within 90 days. It is obvious to me that without a statutory deadline, FDA will continue to delay and delay.

I look forward to hearing the testimony of our witnesses today and at this time I would like to yield to my colleague from Minnesota, who has a special interest in this case, for his opening statement as well as to introduce our first panel of witnesses.

OPENING STATEMENT OF SENATOR COLEMAN

Senator COLEMAN. Thank you, Madam Chairman. It will be an honor to introduce today, Steve and Leslie Lykins, and their daughter Tammy. I want to thank you for calling this hearing.

Twelve years ago, the FDA first studied this issue. Two years ago almost to this day you held hearings on this issue. During those hearings the FDA promised to issue regulations soon. A year and-a-half ago Brian Lykins died, he did not die of complications stemming from the procedure. He was a healthy young man and his death should have been prevented.

His death was followed by national press and CDC studies that once again pointed to the need for national standards. The FDA still has not acted. So today we are revisiting the issue. I suspect we will hear roughly the same testimony we heard 2 years ago. But this time we will also hear from the Lykins family about the death of their son. I can only hope that 2 years from now we do not have to revisit the issue and listen to the same testimony again perhaps with yet another victim whose friends and family had to watch their son or daughter die.

I suspect the problem here is a bureaucratic desire to draft the perfect rule, regardless of the cost in time or lives. I believe in the old 80/20 rule, about 80 percent of the problem can be dealt with with only 20 percent of the effort. It is the last few bits that require the most time. We all agree on certain things like the ability to trace tissue from recipient to donor and back to other recipients, and the need for testing for additional diseases. We could at least get some components in place. No doubt there are more difficult issues that do take a long time to resolve, but why are we still waiting to do the easy stuff, the stuff we know can make a difference?

New York, as the Chairman has noted, has put a law into place which can serve as a model. New York did not wait, nor should we. If nothing else, we can move forward with legislation modeled on the New York law setting up a simple system for testing and tracking. The system could be later augmented by further rules that would allow us to avoid having to return here in 2 years to hear from another family.

Although I will reserve final judgment until I hear from the FDA, it appears to me that this hearing should not have had to be held to deal with this issue. We dealt with it 2 years ago.

Madam Chairman, it is my great but sad honor to introduce today's first witnesses, Steven and Leslie Lykins from Willmar, Minnesota, and their daughter and Brian's sister, Tammy. I wish they did not have to be here today. Brian's death was especially tragic because it occurred after an elective surgery not from medical complications stemming from the procedure itself but rather from a cause that could have been presented if proper regulation had been in effect.

I do not think most people can possibly understand how painful it would be to discuss the death of your children before a roomful of strangers. I want to thank the Lykins for their courage and their commitment for being here today. I want to commend the Chairman for having hearings on this issue. But I also want to remind ourselves that hearings are not always enough.

Madam Chairman, under your leadership, the Permanent Subcommittee on Investigations held a hearing on tissue banks on May 24, 2001, 6 months before Brian's death. But again, as I noted before, the FDA did not take the required actions. It seems to me that the Lykins are doing something we should all admire. Faced with a personal tragedy, their first instinct was to use the painful lessons learned to try and make the world a little bit better.

For our part, we should pledge to them that we will not need to relearn this issue at the cost of someone else's life. Hopefully, and more than hopefully, the FDA will promulgate final regulations

that address the problem. If they do not then we need to, and we will move quickly forward on legislation that the Chairman is bringing forth. One way or another we must honor the Lykins' experience not just by listening to their story but by acting on it.

Madam Chairman, it is, as I said, a great but sad pleasure to introduce Steven and Leslie and Tammy Lykins from Minnesota.

Chairman COLLINS. Thank you very much, Senator. Before I call on Mr. and Mrs. Lykins for their testimony I want to see if my colleague Senator Pryor has any opening comments.

OPENING STATEMENT OF SENATOR PRYOR

Senator PRYOR. Thank you, Madam Chairman.

Thank you all for being here today. Madam Chairman, I am a recipient of an Achilles tendon from a donor bank. I must tell you that was about 7 years ago. I had a very rare and deadly form of cancer in my Achilles tendon. I had great results, but one thing that I took for granted was that the tendon I was receiving out of a donor bank, which happened to be in New Jersey was going to not be tainted and healthy. And it was.

But I must tell you that what I have been reading in preparation for this hearing, I am bordering on outrage at some of the lack of control out there and the lack of supervision. It really is troubling to me. So I really do appreciate you all coming. It takes a lot of courage to be here. I know it is a sad story that you are going to tell. But we are going to do everything we can to listen and try to make the situation better.

Thank you, Madam Chair, for allowing me to speak.

Chairman COLLINS. Thank you, Senator Pryor. I think your experience shows exactly the way most people would react. You would never dream of getting a tissue transplant that you might be putting your life at risk.

Senator PRYOR. That is right.

Chairman COLLINS. Yet properly done and safely done, a tissue transplant can save lives.

Senator PRYOR. Absolutely. It definitely saved my leg. Otherwise I probably would have had to have an amputation. You have so many other considerations at that point. Depending on why you are having the transplant—it could be cancer, it could be any number of ailments, any number of reasons why you are doing it. But you are so preoccupied with that. You always know there is a chance of some sort of tissue rejection. We all know the medical risks there, and the medical community has gotten that risk down to a very low level, a very manageable level. The last thing the patient needs to be concerned about is that he may receive some tainted tissue. Thank you.

Chairman COLLINS. Thank you. Mr. Lykins, I would ask you to proceed with your testimony. Again, thank you so much for being here today with your family.

TESTIMONY OF STEVEN AND LESLIE LYKINS,¹ PARENTS OF BRIAN LYKINS, ACCOMPANIED BY DAUGHTER TAMMY

Mr. LYKINS. You are welcome.

¹The prepared statement of Steve and Leslie Lykins appears in the Appendix on page 39.

In September 2001, our son Brian had arthroscopic surgery to remove a bone chip in his knee. It went very well.

Afterwards, Dr. Mulawka, the surgeon, showed us pictures of Brian's knee which revealed a quarter-size divot in the bone. He told us that Brian should have follow-up surgery in order to prevent future arthritis in his knee. He also explained that a piece of bone from a cadaver would be used in the procedure and told us about the effort and testing that went into ensuring the donated bone tissue would be clean and safe. It was supposed to be a routine surgery, one that Brian could have lived a completely normal life without. In other words, it was strictly a preventative and elective procedure. The recovery from the procedure was expected to take a little longer than the previous one, but no one expected any significant complications.

On Wednesday, November 7, Brian had the follow-up surgery which went well. Dr. Mulawka told us that Brian would become a little sick from the medications and possibly experience more pain than the previous arthroscopic surgery, but otherwise the recovery should go well.

After the operation, Brian was experiencing a lot of pain. He had a horrible headache, upset stomach, and felt like he was burning up. The nurses, however, said his temperature was normal. The doctor decided to keep him overnight for observation. Leslie and I drove home to Willmar for the night. We did not expect any complications so I left for work the next morning and was scheduled to work in Minneapolis for the 5 days.

Ms. LYKINS. After Steve left, I drove to St. Cloud Hospital to pick Brian up. When I got there I found out that he was sick to his stomach and in excruciating pain. The pain pack the doctor had inserted into his knee during the operation apparently was not working. The purpose of the pain pack was to administer medication directly to the knee to help control the pain.

After Brian was released from the hospital I drove him to the St. Cloud Orthopedic Clinic where they removed the pain pack. Brian was originally scheduled to go to the doctor on Friday, the following day, but the doctor thought that he could wait to see Brian until Monday morning. So instead we drove to my home in Willmar where Brian stayed with me overnight. Throughout the evening, Brian began to feel better. His knee was still sore and he felt warm at times, but otherwise he felt fine.

On Friday morning, Brian woke up feeling much better. Of course his knee was still sore, which was to be expected. That afternoon he said he felt well enough to go home. At his home he rested, ate and drank a bit, used the exercise machine they had sent along, and occasionally iced his knee. His recovery was going exactly as we thought that it would. That evening we watched a movie together and he told me that he felt fine and if I wanted to go home I should, which I did.

On Saturday, I had previous plans to be out of the house for most of the day so I was up early. Brian called me, told me that he felt fine, and asked some questions about when he was supposed to take his medication. He said his leg was still sore, but otherwise he felt fine. Then I went out, returned home at about 5 p.m. that night and called Brian. He told me he had been sick to his stomach

for a while, which we had expected. I told him, I would come on over to his house after I took care of a few things and he said that was fine. I got to his house about 6 p.m. As soon as I arrived I realized that he was in worse shape than he had let on. He was throwing up, and told me he almost passed out twice walking to the sink. He complained about feeling warm but he did not feel warm to the touch.

I called Dr. Mulawka's office right away and I got the answering service. They told me that they would call the doctor and have him call me back soon. Shortly after that someone else called from the clinic. When I explained how Brian was feeling, he told me to change the dosage on one of the medications which was likely the culprit of the stomach problems. Brian told me he would like to spend the night at our house so we packed up some of his things and we started to drive to my house which is only two and-a-half miles away.

On the way Brian said he would like to stop at the hospital and have them check him out. We got to the emergency room about 8 p.m. When the nurse and the doctor on duty examined Brian they suspected that he was simply dehydrated and they put him on IV. I think they also gave him something in the IV to help settle his stomach. He still complained about burning up, and he stripped off his shirt and his blankets but he still did not register a fever. Brian also complained about his knee hurting, but the nurse could not find any unusual swelling, redness, or hot spots. A couple of times he doubled over with an upset stomach before the medications seemed to kick in and help him.

The nurse and the doctor thought he would feel better once he was more hydrated from the IV. His vital signs seemed to be OK. The doctor also ordered chest x-rays and had blood drawn. After that was done, Brian was back in his room and he was resting better. No one seemed alarmed about anything at that time and they told us that he would be going home soon. Brian finally appeared to be dozing off to sleep. I was tired and told the nurse that I would go out into the emergency room to get some rest. At that point it was about 1 a.m. in the morning.

I was in the waiting room for about 15 maybe 20 minutes when someone came in and told me to come right away. Brian had suddenly taken a turn for the worse. He had been moved to a larger room in the ER where several people were anxiously working around him. He was awake at that time. After a few minutes, the doctor told me that Brian's vital signs had changed all of a sudden and that they were trying to find out what was wrong. Then the doctor asked me if there was anyone in town who I wanted to call to be with me. I began to worry.

He told me that I should call my husband who, thankfully, was in Minneapolis and not on a trip as he is a pilot. I called Steve and the doctor explained to him that he should come to the hospital immediately, that things did not look good for Brian. I had not expected any of this when I brought Brian to the hospital. We thought he was just dehydrated and nauseous from the strong medicine. The doctors were now planning to move him to the intensive care unit.

I made my way to the ICU when Brian was being wheeled into a room. The doctor was trying to ask Brian questions and he answered them in short little statements. He had not been in the room long when Brian had a convulsion. He sat straight up, gave a loud, long groan. I think that was the point that he went into a coma. The doctors and nurses got me out of the room, attended to Brian, and some time passed. A nurse came and got me and brought me back to Brian's room. I was not in there for long before he had another convulsion. It appeared as though he stopped breathing until the doctor put some sort of respirator on him. I was then led back into the waiting room.

Steven got to the hospital about 4 a.m. The doctor filled him in on Brian's condition and told him they were not exactly sure what was happening but that it was life-threatening.

Mr. LYKINS. Brian was in a coma when I got to the hospital. His blood pressure had been at zero for several hours. All the organs in Brian's body were failing. His heart was the last organ to fail and at 6:21 a.m. our son died.

Shortly after Brian's death we learned that the tissue put into his knee was infected with a deadly bacteria. This infected tissue was allowed to be implanted in Brian's knee due to several industry and government failures.

First, there were no Federal guidelines for the automatic rejection of high-risk cadavers. The cadaver that supplied the tissue for Brian's operation should have been rejected for at least two reasons. First, he died due to suicide so the time of death was uncertain. Second, the body was allowed to remain unrefrigerated for at least 19 hours before tissue harvesting began.

Second, CryoLife procedures for testing and preparing the tissue to make it clean and safe were flawed.

The Centers for Disease Control began an investigation into the cause of Brian's death because two other men from the same area died within about 1 week of each other after having routine knee surgery. One of the men had his surgery in the same hospital as Brian. The CDC found that the other two men died from blood clots. They did not have cadaver tissue put into their bodies. Their knee operations were completely different from Brian's.

However, due to the presence of the deadly bacteria found in Brian's body, the CDC continued with a lengthy investigation into the cause of our son's death. Over the next 6 months I talked on a regular basis with Dr. Kainer from the CDC who was running the investigation. I could not believe the things that I was hearing about the tissue industry as a whole and CryoLife in particular. How could a medical industry in the United States of America be allowed to operate like this? A medical industry allowed to operate with little or no State and/or Federal regulation, how could this be?

The FDA had known about the problems in this industry for years and for some reason was dragging its feet in bringing about the necessary regulations. The CDC had clearly defined the problems in this industry and the FDA would do nothing about it.

It became very clear at that point that the CDC had no power to bring about change in this industry and the FDA was not going to do its job. CryoLife was going to continue to operate in the unsafe manner that caused the death of our son. So at that time we

decided to bring a lawsuit against CryoLife. The purpose of our suit was to bring about change in this company and this industry. Money was never the motivation for the suit. It was only the vehicle that would get people to pay attention.

We did not sue Dr. Mulawka and we did not sue the hospital. We only sued the people responsible for Brian's death because they would not fix the problems on their own. All we ever wanted was for the people involved in Brian's death to learn from what happened and fix the problems. It became clear that CryoLife and the FDA would not fix the problem without the lawsuit. Less than 30 days after we filed the suit, the FDA shut CryoLife down due to their unsafe practices. Unfortunately, there are still no Federal regulations to prevent companies like CryoLife from operating in unsafe ways.

One and a half years after Brian's death, the FDA is still only proposing regulations for the tissue industry. Nothing has changed. The tissue industry can still operate any way they want with little or no Federal regulations. What is taking the FDA so long? In our lawsuit, we listed seven areas of meaningful reforms that are needed in this industry. First is rejection of high-risk cadavers such as diseased cadavers that have cancer, meningitis; cadavers that are over 70-years-old; cadavers unrefrigerated for over 10 hours; suicide cadavers.

Second, testing of tissue when cadaver is received.

Third, sterilize tissue before distribution.

Fourth, discard cadaver if any contamination is found.

Fifth, mandatory reporting of contamination to Federal agencies and the end-user doctor.

Sixth, certification of cadaver harvesting personnel, uniform basic qualifications and uniform training.

And seventh, mandatory annual procedure and inventory audit.

Had these reforms been in place at the time of Brian's operation, our son would not be dead and many other people would not be dealing with some very serious medical conditions. How much longer is it going to take the FDA to do its job and bring the tissue industry into the 21st Century? This industry has been allowed to operate like something out of the Wild West for too long. Too many people have had their lives ruined and too many people have died. We need reforms and regulations in this industry now, not some day. There is no question that the tissue industry is necessary and important for the advancement of quality of life. However, there is no need for it to operate in such a dangerous manner.

Chairman COLLINS. I want to thank you both for your very eloquent testimony. I know I speak for everyone in this room when I say that I am so sorry for your loss. My hope is that by your coming forward that we have put a human face on this problem, and that it will prompt the FDA to act. I just want to pledge to you that I am going to ensure that they act. We have given them too long already and I believe that your experience and your moving testimony will help convince our colleagues that far too long an amount of time has passed already and that we do need prompt action.

You mentioned that prior to Brian's surgery that there was a discussion with his physician about the transplanted tissue. Now I know that anyone undergoing any kind of surgery signs a standard

informed consent form, but was there any discussion of possible risks of the tissue itself, Mr. Lykins?

Mr. LYKINS. Dr. Mulawka sat with my wife and I and Brian and we talked about that and he explained over—it was quite a lengthy explanation of all of the safety standards that went into ensuring that the tissue was safe. After he finished explaining that to us, we were very confident that the tissue was going to be clean, that there would be no problems. It was never even a consideration that the tissue may not be safe to be put in Brian's body.

Chairman COLLINS. Did you assume at that time that as with organ transplants, as with medical devices, that there was Federal regulation of the tissue industry so that you really did not need to worry about the safety, Mrs. Lykins?

Ms. LYKINS. Yes, we did, at that time. We just assumed, which now from hindsight we know better, but that just like any—like the organs and such, that these things were already handled through the medical field and knew them to be safe.

Chairman COLLINS. I think that is a very logical assumption for you to have made. It is one that I think most health care professionals made, including the physician. The surgeon who treated your son obviously assumed that there was a process in place to ensure the safety of the transplanted tissue.

How did you learn of the cause of Brian's death, Mr. Lykins?

Mr. LYKINS. When Brian died, the doctor in the ICU, even when he died they said, we do not know what happened. So we talked with him and we ordered that they do an autopsy on Brian to find out the cause of what killed him. That is where we started the learning process was from that autopsy.

Chairman COLLINS. When did you learn that the cadaver from which the tissue had been taken had been left unrefrigerated for at least 19 hours, clearly raising the risk of infection and other problems?

Mr. LYKINS. During that next 6 months after Brian's death when we were in contact with—first it started with the Minnesota Department of Health and then it went to the CDC, that is when we started learning things like that. It was sometime during that investigation that the fact that it had been unrefrigerated for 19 hours came up.

Chairman COLLINS. During the course of your lawsuit against the tissue bank that procured and processed the tissue for Brian, which is CryoLife, did you learn of any previous complaints against the company or other problems that CryoLife had experienced?

Mr. LYKINS. Yes, there were at least two of them that we were familiar with. One, and I cannot remember the gentleman's name but he is out in the San Francisco area that a couple of years before Brian's death he had a knee operation where he received tainted tissue which caused him some real severe medical problems.

Chairman COLLINS. Is there anything that you have learned from this experience that particularly concerned you?

Ms. LYKINS. I think it probably would be in the medical field in dealing with this is that we did not have the information and that our doctors did not have this vital information that was so needed.

Mr. LYKINS. Of course we have done a lot of talking with friends and family and even acquaintance at work about it and the thing

that I really struggle with is if they had given us a document when we went in for this operation that said that the tissue that your son will be receiving is not regulated, in fact we do not know where it is coming from, we have no standards for how it is produced, we cannot guarantee it is going to be safe, and there is a risk of death or serious infection from this we would, of course, have said, no, we were not going to do that operation. We were not given that option because nobody knew that at the time.

So the fact that we were not given that option, but we assumed, like every other part of the medical industry, that it is regulated, when it is a public safety thing—that companies just cannot operate like that where they can pose a serious health risk. I cannot think of any industry—I am a pilot and you look at the high regulation in the airline industry and you look at all the other areas where we have such good safety standards in place and then to see this one with none, I think that is the part that has bothered us the most.

Chairman COLLINS. I am going to yield to Senator Coleman at this point because I know he is on a very tight schedule.

Senator COLEMAN. Thank you, Madam Chairman. I am not going to ask any questions. I hope to have an opportunity to visit with the family a little later. My daughter and her class are in my office and I am going to go down there and see them in a couple of minutes.

But I do want to note, in their testimony the Lykins said their purpose here was not to sue people for money. It is to fix the problem. I will say to them publicly what I said privately, that the Chairman is very serious about this issue, and that something will come from this testimony today. So your purposes will be achieved and I just want to again thank you for your courage and your commitment.

Thank you, Madam Chairman.

Chairman COLLINS. Thank you, Senator. I just have one more question before I yield to my colleague and one comment. When we met yesterday, just to expand on your last response, you told us that if there were a sign up in the operating room or a form given to a patient saying, warning, the transplant you are about to receive has no safety guarantee it all. The Federal Government does not really regulate it. Unless you are living in one of three States there is no State regulation. Proceed at your own risk. That your son would not have proceeded with this operation. Indeed, it would be the end of the tissue bank industry, which is unfortunate because there is a lot of good that comes from tissue transplants.

But I think that you are absolutely right and that only makes the case for effective regulation even stronger, because we want to make sure that transplanted tissue which literally can save lives, does not take lives. That is what this is all about.

My final question for you is, we will have a representative from the FDA testifying before us today. In his defense, he has only been on the job for a few months. He is new to his position. But this is an indictment of the agency for failure to act. I just want to ask you if there is any question that you want me to pose to the FDA representative today? Mrs. Lykins.

Mrs. LYKINS. I think what we have put in here is, how can the American public, the people, the patients that are needing this help, how can they turn their back and oppose some safety that these people can rely on and know that they will indeed be getting tissue that will be helping them in their life?

Chairman COLLINS. Thank you. Mr. Lykins, do you have anything to add?

Mr. LYKINS. I guess I really do not. In our statement we have said it. We just do not understand why this is taking so long. We have heard at least two or three times since Brian died, and statements before that, just one more year, just one more year and we will have it done. We just heard that again recently, just one more year. It does not seem like it is that hard to get some kind of, like Senator Coleman was saying, let us get the basic framework in place. New York has it right now. If nothing else, let us adopt New York's and get it started. But there are people that are at serious risk today having these operations that do not even know about it. We have got to get something going here.

Chairman COLLINS. Thank you. Senator Pryor.

Senator PRYOR. Thank you. Again thank you all for being here. I have a factual question about your case and that is, CryoLife, is that a private company? Is that an association? Is that a for-profit company? Is that a lab? What is that or what was that?

Mr. LYKINS. It is a for-profit corporation and they do a lot of different things and part of the things that they do is they supply this tissue.

Senator PRYOR. Did I understand what you said a few moments ago that they are no longer in business?

Mr. LYKINS. No. Just shortly after we filed this suit the FDA went in and stopped, shut down their tissue processing part of their business. They were stopped from doing that except in life-threatening circumstances until they got their house in order. I forget exactly how long but they eventually did comply with the FDA's request so they are back operating now.

Senator PRYOR. Tell me about your contacts with the FDA. It sounds like you had some litigation going and you have also had some contacts with the Food and Drug Administration. I would like to zero in on your contacts with the FDA. Give me a feel for how you have communicated with them. Is it by letter, by phone call, by personal visit? How have you communicated with FDA?

Mr. LYKINS. We have not personally communicated with the FDA at all. Our attorneys, during the lawsuit there was communication there, but we have never personally communicated with them.

Senator PRYOR. Has the FDA taken steps to keep either you or your attorneys advised about the status of the process within the agency?

Mr. LYKINS. Not that I am aware of.

Senator PRYOR. Have they ever been proactive in any way with you to try to give you any kind of assurance that they are working on this problem as quickly as they can? Are they going to try to move things out as quickly as they can to prevent this from happening in the future?

Mr. LYKINS. No.

Senator PRYOR. This incident occurred in 2001?

Mr. LYKINS. Yes.

Senator PRYOR. How old was your son?

Mr. LYKINS. He was 23.

Senator PRYOR. You made a statement about this industry, that it is analogous to the Wild West. When you say that, do you mean that your concern is it is totally unregulated and there is no government supervision about what is going on out there, or at least it is very limited?

Mr. LYKINS. The symbolism behind that statement was, I see this industry as operating like a bunch of Wild West gunslingers that are just shooting from the hip, doing it any way they want to do it, and with no laws or regulations they are just making it up as they go. That was the thinking behind that statement.

Senator PRYOR. Have you been in contact with other families who have had similar experiences?

Mr. LYKINS. We have had several families that have called us and talked to us, yes. Yes, we have.

Senator PRYOR. One last question on the nature of the bacterial infection. What was the origin of that bacterial infection? Was it because the tissue was not handled properly? Or was it pre-existing in the cadaver? Do you know?

Mr. LYKINS. The bacteria is called *Clostridium sordellii*. My understanding of it is it is a spore-based bacteria, which to me means it is in a little, kind of like an egg shell. It is a normal part of a decomposing body. It starts in the intestines and then moves out into the body over time. That is where the time issue is such a big deal. So it was not a pre-existing. It was allowed to—

Senator PRYOR. It is naturally occurring if proper steps are not taken to prevent it?

Mr. LYKINS. That is right.

Senator PRYOR. Madam Chair, that is all I have.

Chairman COLLINS. Thank you very much, Senator Pryor.

I want to thank you so much for your very courageous and moving testimony. I want to thank Tammy for being here as well. If you have anything that you feel that your parents forgot to say today or that you would like to add I just wanted to give you the opportunity. If you feel it has been covered, that is fine too.

Ms. TAMMY LYKINS. I think they covered it.

Chairman COLLINS. Thank you. Again, thank you so much for sharing your story with us. All of us simply cannot imagine the pain and anger you must have endured. But I want to tell you that we are committed to working with you to make sure that no other family goes through what you have gone through. That is our goal and I know it is yours as well. So thank you so much for being with us today.

Mr. LYKINS. Thank you.

Chairman COLLINS. I would now like to call forward our second panel. Our first witness on the second panel will be Dr. Steven Solomon. Dr. Solomon is the acting director of the Division of Health Care Quality Promotion at the National Center for Infectious Diseases which is part of the Centers for Disease Control and Prevention. We also will be hearing from Dr. Jeanne Linden, the director of Blood and Tissue Resources for the New York State Department

of Health. We want to thank both of you for your willingness to participate today and, Dr. Solomon, I would ask that you go first.

TESTIMONY OF STEVEN L. SOLOMON, M.D.,¹ ACTING DIRECTOR, DIVISION OF HEALTHCARE QUALITY PROMOTION, NATIONAL CENTER FOR INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. SOLOMON. Thank you. Good morning. I am Dr. Steven L. Solomon, acting director of the Division of Healthcare Quality Promotion in the Centers for Disease Control and Prevention's National Center for Infectious Diseases. Thank you for the opportunity to report to you on CDC's activities with regard to the problem of infections occurring in association with the surgical implantation of human tissue. As a physician and as a parent, I want to express my sympathies to the Lykins family for their tragic loss.

An allograft is human tissue which is recovered from cadavers and processed before being transplanted into another person. The most common type of allograft is bone. Tendons, skin, heart valves, and corneas are other common types of human tissue allografts. Allografts may be lifesaving and can substantially improve the quality of life for many patients, reducing disability and restoring mobility or sight. The use of allografts has increased dramatically in recent years.

As with any surgical procedure, the implantation of human tissue allografts may be associated with complications, including infections at the surgical site. Although rare, some of these infections are associated with bacterial contamination of the implanted allografts, a complication that can result in serious morbidity and death. In collaboration with the Food and Drug Administration, the Health Resources and Services Administration, and other partners, CDC continues to investigate reports of infections and assess the need for possible changes in the processing and quality control methods for allografts as a means of preventing allograft associated infections.

As indicated, transplanted tissue is commonly obtained from cadaveric material. After recovery from the cadaver, allografts may be either sterilized or undergo aseptic processing without sterilization. In aseptic processing, careful handling ensures that no new organisms are introduced during the recovery of tissues from the cadavers. Tissues may be treated with chemicals or antibiotics to minimize intrinsic contamination, that is, bacteria that contaminate these tissues following death and prior to, or during recovery of, the tissues. Thus, the tissue is not sterilized. The processing is intended only to reduce intrinsic contamination and prevent further contamination of the tissue.

In November 2001, CDC began an investigation after receiving a report from the Minnesota Department of Health of a fatal case of infection with *Clostridium sordellii* bacteria in a young man who had recently received a bone cartilage allograft. *Clostridium sordellii* bacteria were identified in cultures of this young man's blood obtained prior to his death. Investigators at CDC contacted

¹The prepared statement of Dr. Solomon appears in the Appendix on page 44.

the tissue bank from which the transplanted allograft had been obtained and the tissue bank provided CDC with samples of non-implanted tissues from the same cadaveric donor. CDC laboratories identified *C. sordellii* bacteria in some of these tissues. As a result of this investigation, CDC concluded that this young man's infection had resulted from intrinsic bacterial contamination of the transplanted cartilage tissue.

CDC subsequently contacted the health care providers of all patients who had already received transplanted allografts from this same donor to determine if other infections had occurred. CDC found that tissues had been transplanted into nine patients located in eight States. One of these patients developed an infection following the surgical procedure. This patient's infection was successfully treated with antibiotic therapy and the patient recovered.

To follow up this investigation, CDC, in collaboration with FDA, requested that cases of allograft-associated infections be reported to CDC through State and local health departments in addition to the reporting of such cases to FDA. Cases reported to FDA were shared with investigators at CDC and State health departments. As of March 2003, 62 reports of allograft-associated infections had been reported to CDC. Ninety-three percent of these infections were associated with musculoskeletal tissues. Cases of infection were reported from 20 States and involved tissues that had been treated at 12 different tissue processors. These surveillance findings have been shared with FDA, the American Association of Tissue Banks and others.

In addition to investigating infections associated with bacterial contamination of allografts, CDC has investigated reports of infections caused by fungi, parasites, and viruses following transplantation of organs and tissues. Examples include the transmission of hepatitis C from a bone allograft, and transmissions of West Nile virus and Chagas disease, a parasitic infection, following solid organ transplantation.

CDC believes that the best way to reduce the risk of infectious agents associated with tissue transplants is to develop new methods of sterilizing tissue that do not adversely affect the functioning of the tissue when transplanted into patients. Every effort should be made to use suitable sterilization methods. However, if that is not possible, every effort should be made to minimize the risk of intrinsic bacterial infection. Recovered tissue should be cultured before suspension in anti-microbial solutions, and if bacteria commonly found in the human bowel are isolated, all tissue from that donor that cannot be sterilized should be discarded.

Other public health interventions that will greatly facilitate the prevention and control of infections associated with tissue and organ transplantation are enhanced surveillance and enhanced communication with clinicians. Addressing the problem of infections associated with tissue and organ transplantation is part of the larger problem of patient safety requiring significant changes through all parts of the health care industry.

Organizations involved in organ and tissue procurement, and suppliers and processors of tissues must put in place assiduously-followed procedures to assure that any risks associated with tissue transplantation are greatly minimized, if not completely elimi-

nated. State and Federal public health authorities must continue to enhance their ability to collect, analyze, interpret, and disseminate information about potential patient safety hazards due to biological products, medical devices, and medical procedures.

Clinicians and medical professionals must, with our help, increase their awareness of specific patient safety problems and fulfill their role in reporting such problems promptly to the appropriate authorities so that necessary public health action can be taken. CDC, FDA and other partners, as noted earlier, are actively engaged in ensuring that biological products, including tissue allografts are as safe as possible.

Thank you so much for the opportunity to present this information to you today. I am happy to answer any questions that you may have.

Chairman COLLINS. Thank you, Dr. Solomon. Dr. Linden, welcome.

TESTIMONY OF JEANNE V. LINDEN, M.D.,¹ DIRECTOR, BLOOD AND TISSUE RESOURCES, WADSWORTH CENTER, NEW YORK STATE DEPARTMENT OF HEALTH

Dr. LINDEN. Thank you. Good morning Members of the Committee. My name is Jeanne Linden. I direct the New York State Department of Health's Blood and Tissue Resources Program. New York State has spearheaded development of many innovative programs and maintains an active regulatory oversight in many important areas of public health. Since infected tissue poses the risk of pathogen transmission to recipients, oversight of tissue banking activities is an essential component, we feel, of any comprehensive public health regulatory program.

In addition to the well-known risks associated with viral and prion-associated diseases, bacterial infections in recipients of aseptically processed cadaveric tissues, and infections with emerging agents such as West Nile virus, possibly SARS, are also of grave concern.

In New York State regulation of tissue banks began with adoption of standards for hematopoietic stem cell banks in 1988, for semen banks in 1989, and for human milk banks in 1990. In 1991, a successful comprehensive tissue bank oversight program was developed and instituted in New York. Comprehensive rules set standards for donor medical history assessment, and evaluation of risk factors for disease transmission, laboratory testing, and record-keeping to ensure the ability to track disposition of donated tissue from donor to recipient and vice versa. These standards were formulated based on the medical literature, consensus of experts in the field, and existing standards of professional organizations such as the American Association of Tissue Banks, the Eye Banks Association of America, and the American Society for Reproductive Medicine, which at that time was known as the American Fertility Society.

Technical requirements are in place for all human tissues intended for transplantation, also for research or education, including

¹The prepared statement of Dr. Linden with an attachment appears in the Appendix on page 55.

cardiovascular tissue, musculoskeletal tissue, skin tissue and eye tissue. Licensure requirements for tissue banks apply to all facilities that collect, process, store, or distribute, or transplant tissue in New York State. At present, 736 tissue banks are licensed to operate in the State, including more than 130 facilities located outside the State. The table included with my written statement enumerates the various types of tissue banks that are licensed to operate in New York.

Comprehensive tissue banks include cardiovascular, musculoskeletal tissue banks, skin banks, eye banks, semen banks, oocyte donation programs, bone marrow collection centers, umbilical cord blood banks, human milk banks, and non-transplant tissue banks, which is what we call tissue for education and research purposes.

In New York State, facilities that use tissues clinically, including hospitals, ambulatory surgery centers, and even physician's offices are subject to tissue bank licensure as well as the specific administrative recordkeeping and quality assurance requirements. Errors and accidents detected after distribution of tissue as well as adverse events must be reported to the Wadsworth Center of the State Health Department within 7 days of discovery, affording another mechanism for effective oversight. Licensed tissue transplantation facilities must report any adverse events and patients that might be linked to the tissue.

From the very inception of the New York licensure program staff identified unacceptable practices going on in tissue banks. In one case, two semen bank operators were using only themselves as donors but through the use of fictitious names led physicians and recipients to believe that more than a dozen donors were available through the program. Testing and recordkeeping at this bank were virtually non-existent. We actually needed to wind up following the money and subpoena bank records to track that case.

Another reported incident concerned a hematopoietic stem cell bank that transmitted the wrong component, that is the ABO incompatible red cells that had been removed from the bone marrow rather than the marrow itself. Had the marrow not been retrievable, the patient, who had already undergone ablative therapy, could have died as a result of a severely impaired immune system. One surgical bone bank lost the skull flap of an autologous donor. These cases demonstrate the crucial importance of thoroughly identifying tissues used for transplantation.

The death of Brian Lykins in November 2001 brought the inherent risk of using aseptically processed allografts to national attention. This tragic event spurred an immediate investigation that has been described by my colleague. In cooperation with State health departments, the CDC was able to locate non-transplanted tissues from the same donor and identify the bacterium. A second recipient from the implicated donor also developed an infection but cultures had not been done. I apologize, my written statement is incorrect in that regard. They were not done. They were not negative. This patient, fortunately, responded to antibiotic treatment.

The CDC investigation determined that CryoLife, the tissue bank involved, at that time routinely cultured allograft tissues following suspension in an anti-microbial solution, which was not acceptable. Such a culturing protocol can lead to false negative results because

of the bacteriostatic nature of certain bacteria, particularly spore-forming anaerobes like *Clostridium*.

In February 2002, absent its own jurisdiction or assistance from any other Federal agencies, CDC asked the New York State Department of Health's assistance in obtaining records and seeking additional tissue samples from the donor implicated in the Lykins case that remained in CryoLife's inventory, as well as records and tissues from donors implicated in other allograft-associated infection cases. The enforcement authority of the New York State Commissioner of Health enabled the Blood and Tissue Resources Program surveyors to conduct an on-site inspection of the tissue bank where several deficiencies were noted, including the failure to perform recovery culture testing. The Wadsworth Center, the department's public health laboratory, isolated *Clostridium septicum* in tissues from two donors implicated in allograft-associated *Clostridium* infections. No remaining tissues associated with the Lykins case donor were found.

The department also assisted CDC in identifying potential additional cases of post-transplant allograft infections by contacting physicians who had used tissue from implicated donors for transplantation. Since confidentiality requirements prohibited us from sharing the patient names with CDC, we needed to contact these physicians directly.

The number of allograft-associated *Clostridium* infections per one million population was found to be statistically significantly lower in New York State compared to the remainder of the country; 0 vs. 0.06 per million with a highly significant p-value of 0.0009—highly significant.

CryoLife maintained two inventories of tissue for release; one suitable for New York State patients and a second one for patients in other States. Tissues from only two of the implicated donors would have met the requirements for tissue in the New York inventory. Tissue from six of the donors, including the donor in the Lykins case, would have been disqualified for distribution to New York. This likely contributed to explaining why there were no known cases of allograft-associated *Clostridium* infections in New York. We believe that New York State regulations have played a significant role in protecting the State's patients from such adverse transplant-related outcomes.

Based on our experience, we believe that a mechanism to ensure documentation of disposition of all tissues must be established and enforced so that donors may be traced in cases of adverse events, and all recipient outcomes must be reviewed and followed up as necessary. The 1985 LifeNet incident, which was discovered and reported in 1991 in which numerous tissues were distributed from a donor in the window period of HIV infection, illustrates the need for accurate accounting for all allografts distributed by a tissue bank and issued for transplant by the hospital. In this case, 6 of 54 distributed tissues could not be accounted for by the transplanting hospitals.

New York State's rigorous requirements for licensure and record-keeping by transplantation facilities are aimed at ensuring accurate tracking to each recipient. States that operate tissue bank oversight programs complement Federal efforts in this most impor-

tant public health area. New York State has established a partnership agreement in place with the FDA's New York District to share inspection documents, and other reports and documents, and minimize duplicated effort.

We commend your endeavors to address this critical public health concern. While tissue banking is clearly in need of Federal oversight and uniform minimum standards, any potentially deleterious effects of imposing overly restrictive standards on the tissue supply, we believe must be balanced against the proven benefits of such standards to the public health. Specifically, it is unrealistic to expect tissue banks to be able to guarantee the absence of contamination in a donor when tissues are processed aseptically. It must be acknowledged that since some tissues are in short supply, patients' health could be adversely affected if potentially draconian regulations further diminish the tissue supply.

The FDA's existing rules for tissue banks and progression toward good tissue practices represent a valuable step toward enhancing tissue bank oversight nationwide. The established benefits of such standards in this area are abundantly clear. The New York State program has identified several cases in which unsuitable donors have been rejected and recipients thus protected by adherence to the State's rigorous standards. However, we do remind you that any regulatory scheme must remain flexible enough to quickly adapt to the rapidly escalating changes in this field.

Thank you very much for the opportunity to comment.

Chairman COLLINS. Thank you, Dr. Linden. Your testimony is very helpful to us and I want to congratulate New York State for coming up with a regulatory framework that has helped protect patients in your State.

There are two points in your testimony that I want to explore a little further with you. First, I find it astonishing that CryoLife actually kept different batches of processed tissue in its supply; those that were suitable for New York State and those that could be used elsewhere. That may not be illegal but it certainly is questionable that different batches of tissues are sent to a State with a good regulatory scheme than are made available to States, and that is the vast majority of States that do not have a regulatory framework in place.

Do you think that this is an isolated example or do you think that other tissue banks may also have separate procedures that are followed if the tissue is going to New York State?

Dr. LINDEN. The majority of tissue banks, the 130 licensed outside New York, use the same standards for everybody. They do not have separate inventories. I cannot say whether CryoLife was the only one. There may be a small number of others, but the majority just meet our standards for everyone. But from a legal standpoint we need to allow that because our jurisdiction is protecting the people of the State of New York.

Chairman COLLINS. But in the case at least of CryoLife, CryoLife was doing different procedures to meet your stricter standards and thus, I would argue that the patients in New York State were at less risk of getting contaminated tissue, as the complicated study, which I am not sure I followed on p-values, seems to indicate. Is that a fair statement?

Dr. LINDEN. We believe that is the case and we believe that everyone in the United States should benefit from the same standards. We do not encourage facilities that have two different inventories, but we do allow it.

Chairman COLLINS. The second point that I want to follow up with you on to make sure that the Committee fully appreciates what you said is, you said in your statement that absent its own jurisdiction or assistance from other Federal agencies, that the CDC had to come to New York State public health officials in order to conduct the investigation into Brian Lykins' death; is that correct?

Dr. LINDEN. For Brian Lykins' case, no, they were able to handle that with the Minnesota and Georgia State health departments, and it is my understanding the facility cooperated fully in the Lykins case. It is when they got into looking into other reported infections, which exceeded 25 eventually, at that point the facility was no longer willing to voluntarily cooperate, so an agency with authority was needed, and we in fact did have to use our subpoena power.

Chairman COLLINS. But I think your point is, and I am reading from your testimony on page 3 and it actually refers to the Lykins case as well, that in order to get the additional samples that the Federal Government did not have adequate authority; is that accurate?

Dr. LINDEN. You probably should be asking my colleague.

Chairman COLLINS. Actually, why don't I ask Dr. Solomon that. Is it difficult for the CDC in a case like this where the tissue bank is under no legal obligation to report adverse events and to cooperate with you, to do the kind of tracing and careful investigation that needs to be done?

Dr. SOLOMON. Yes. Throughout this investigation there was an obvious sense of urgency to identify any risks to health and safety. From the outset, CDC was working closely with a number of partner public health organizations, including the State health departments as mentioned by Dr. Linden and the FDA. At each stage of the investigation we had the opportunity to call on the resources of these public health partners who do have the authority, the legal authority to obtain information and materials.

We were very fortunate that Dr. Linden and her staff have a very experienced and very proactive program so that at one point, obtaining some documents and specimens through the resources and capabilities of the New York State Department of Health was the most expeditious and the quickest way of obtaining that material. We are very appreciative of her efforts, as we are of the efforts of the other partners, including the Minnesota and Georgia health departments and the FDA. That kind of close collaboration is critical for all of our investigations.

Chairman COLLINS. Dr. Solomon, you mentioned in your testimony that in the course of the investigation that you discovered that there had been tissue donation from this one cadaver that went to nine patients in eight States; is that correct?

Dr. SOLOMON. That is correct, yes.

Chairman COLLINS. Indeed, in just the Brian Lykins case there are three States involved. The tissue came from a donor in Utah.

It was processed in Georgia, and the surgery was in Minnesota. Is that accurate?

Dr. SOLOMON. Yes, it is.

Chairman COLLINS. Does this not make a strong case for uniform Federal regulations?

Dr. SOLOMON. We are eager to see any kind of regulation or other type of activity which will help reduce the risks to patients. We are very grateful that New York State has that type of regulation in place.

Chairman COLLINS. One more question, Dr. Solomon, before I yield to my colleagues. I have a list that our Committee obtained from CryoLife of some 20 cases involving tainted tissues or allegations of tainted tissues. Eighteen of these 20 ended up in some sort of court case in lawsuits. Under the existing regulations, it is my understanding that CryoLife has no obligation to report these 20 cases to the CDC or the FDA. Do you believe that there should be a Federal requirement for adverse events to be reported? Should there be mandatory reporting of adverse events by tissue banks?

Dr. SOLOMON. We have dealt with the issue of mandatory reporting more broadly on the patient safety front for sometime. CDC gets most of its surveillance and other reporting through State health departments and directly from health care providers or patients as well as health care facilities. Manufacturers and other processors more routinely do their reporting to FDA. I think it would be more appropriate for FDA to comment on their relationship with manufacturers and tissue processors.

Chairman COLLINS. Senator Pryor.

Senator PRYOR. Thank you. Dr. Solomon, if I can follow up on something you said a few moments ago about New York. You mentioned you are grateful that New York has standards in place. Are you pretty familiar with those standards?

Dr. SOLOMON. I am not intimately familiar with New York State's standards specifically.

Senator PRYOR. Do you think that the New York standards should be adopted as the national standard?

Dr. SOLOMON. My familiarity with the New York standards specifically are not sufficient for me to comment on whether all of those should be adapted as national standards. Clearly, as Dr. Linden testified, the New York standards do protect patients in New York State. Specifically, whether those standards would be applicable point by point federally is something that I just do not have information on at this time.

Senator PRYOR. Dr. Solomon, I know you are not completely familiar with them, but is there anything in the New York standards which you would change, or you think is unnecessary, or that you would strengthen? Are you aware of anything, given your limited knowledge of them, that you would change about the New York standards?

Dr. SOLOMON. I am not aware of them sufficiently to be able to say specifically if there are elements that would not be adaptable. But from what I understand from Dr. Linden, many of those standards are consistent with what both CDC has proposed and FDA has proposed throughout this investigation.

Senator PRYOR. That is fair. I know that you are not holding yourself out to be extremely knowledgeable of those standards. I understand that.

Dr. LINDEN, let me ask you about New York's standards. Do you consider them the most stringent and the most thorough in the country?

Dr. LINDEN. We like to think so.

Senator PRYOR. Do you think they should be adopted as the national standard?

Dr. LINDEN. They certainly could not be adopted—the statutory authority the FDA has is completely different from ours, so the format needs to be different. I think that certainly to the extent that our standards capture the accepted practice in the community, justified in the medical literature, that many of those elements would be important to be included with the FDA's approach, and indeed they are.

Senator PRYOR. Are you aware of any holes in the New York standards that you think the State of New York should fix?

Dr. LINDEN. Certainly, we are always looking to improve our regulations. We, in fact, have been actively working with the associated medical schools in New York to strengthen considerably the technical standards for the use of whole bodies in medical education where we have had few standards in the past.

On the transplant side, certainly we continue to watch for improvements in technology, possible availability this summer of testing for West Nile virus. We are always looking to improve. I cannot think offhand of a specific hole, with the exception of making the comment that we really regulate services, the people who collect and process and distribute the tissue, and the users, which we feel is a critical part of our program which I believe FDA might not even be able to reach under their authority. FDA regulates products.

So as I said, the approach is different and they have emphasis on certain issues like validation that is a little bit different from our approach.

Senator PRYOR. Now walk us through that here for just a moment. Explain the point you are making about the critical nature of this.

Dr. LINDEN. We have found that the users, that is the transplant sites—

Senator PRYOR. Now when you say users, do you mean the doctors who are performing the transplant?

Dr. LINDEN. Yes, the hospitals, the ambulatory surgery centers, and physicians' offices that are actually transplanting or using these tissues, to make sure that they do not get them mixed up, which has happened, that they go to the right person, that there is adequate informed consent. I made the point that some of these tissues, including the type of femoral condyle used in Mr. Lykins' surgery, cannot withstand, at the present time, the types of viral and bacterial inactivation methods that are available, such as gamma radiation. Maybe there will be other processes in the future.

But some of these tissues are very valuable. If we simply eliminated them, orthopedic surgeons would be very upset, and patients

would not be able to get the type of life-enhancing surgeries they have. But we feel that the informed consent, so that the recipient knows the risks and in consultation with the physician can weight those is very important. So that is one of the emphasis of our program.

Senator PRYOR. On a typical tissue—and I know that this may be an unfair question because there are lots of different kinds of tissue. But how many tests are done, say on a bone that is going to be transplanted? How many tests are done on that? Is that an easy thing to do? Is that an expensive thing to do? What are we talking about here?

Dr. LINDEN. Are you talking about testing of the bone itself or of the donor?

Senator PRYOR. That is a good question. Both of those. How do you do that?

Dr. LINDEN. The donor's blood, and a pre-mortem specimen is preferable, is tested for a lot of the same things that blood donors are tested for, plus a few more, particularly depending on what the tissue is. A particular concern today since we are talking about bacterial contamination, a culture of a sample taken at the time of recovery of the tissue and before the tissue is subjected to antimicrobial solutions is something that we require and was absent in some of the cases that we have talked about here today. So that would be testing of the tissue itself.

In the case of eye tissue, for example, there needs to be an analysis using a slit lamp to determine whether it is suitable for transplant and that sort of thing. These are tissue-specific tests that are done to heart valves. There are slightly different things.

Senator PRYOR. Thank you, Madam Chairman.

Chairman COLLINS. Thank you. Senator Carper.

OPENING STATEMENT OF SENATOR CARPER

Senator CARPER. Welcome. How are you? Thanks for joining us today.

Dr. Solomon, that is a nice-looking uniform you have got on. I almost saluted when I came in. Are you a captain as well?

Dr. SOLOMON. Yes, sir.

Senator CARPER. I used to be a captain in the Navy. Whenever I see your folks walking around in uniforms it brings back some good memories. But I was never a doctor.

I missed your testimony. I was involved in another meeting right out in the anteroom with other doctors from Delaware who are here. We talked about an issue, actually an issue involving medical malpractice. The question is whether or not that is something that States should deal with or we should deal with it at the Federal level. It sounds to me, Dr. Linden, you have decided in New York to deal with the issue of handling of tissue and the safe use thereof, try to deal with it on a State level instead of waiting for us in Washington to come up with regulations. Is that correct?

Dr. LINDEN. Yes. We really got started in the tissue in the mid 1980's, I think largely as a result of the HIV crisis which was particularly acute in New York and there was really recognition that tissues are yet another way that infectious diseases could be spread.

Senator CARPER. Are there other States who have followed suit or preceded you with development of some of the kinds of regulations?

Dr. LINDEN. I believe we were the first, but Florida—

Senator CARPER. It is good being first. That is a motto in Delaware, it is good being first.

Dr. LINDEN. Yes, it is good to be first. Florida also has a comprehensive program, although it does not cover reproductive tissues is my understanding. California also has a law, but last I heard their technical standards had not been adopted yet. There were some issues there. Other States such as New Jersey do certain of the tissues. I believe ours is the most comprehensive and it was the first.

Senator CARPER. In my old job as Governor of Delaware I was the chairman of the National Governors Association and I always used to say that States ought to be laboratories of democracy, and in some cases States will come up with a particular approach, could be welfare reform, could be education, that might serve as a role model for us on a national level. Is there any reason to believe that what you have developed in New York or in some other State could be a role model for us, or a model for us to try to replicate at a national level?

Dr. LINDEN. I do not think it can be replicated as is, but certainly many of the components can be and in fact have been. We have shared our regulations with FDA, and I have served on some of their advisory committees. We have worked with them closely. As I mentioned, we have a partnership agreement with the district office. I believe that they have in fact considered some of our suggestions and incorporated them into their existing regulations and proposed regulations.

Senator CARPER. Given what you have learned in the development and implementation of your regulations, what lessons are there for us at the Federal level, major lessons for us at the Federal level that you would like to leave me with today?

Dr. LINDEN. Certainly checking everything and not making assumptions is very important. You cannot just adopt the standards and just think that everybody is going to follow them. They might not know about them, particularly when you are getting into regulating physicians, which is actually an area we are getting into. So that everything really needs to be verified. We think the on-site inspection process is very important.

Senator CARPER. How does your enforcement mechanism work? Or do you have enforcement mechanism?

Dr. LINDEN. Yes, absolutely. Routinely, following a survey we will cite deficiencies and usually they are correct. For egregious situations such as one that I described in my testimony of two young men operating a semen bank using only themselves as donors, we filed charges. We have filed charges in some cases where there are improprieties or very severe deficiencies that are not corrected.

Senator CARPER. Thanks. Dr. Solomon, I missed your testimony, as I said earlier, and I would appreciate it if you would just take maybe a minute or so and just recap for me the most important things that you would want us to garner from your contributions.

Dr. SOLOMON. Certainly. Thank you. The main issues have to do with both our ability to conduct investigations, to follow up on investigations, and to encourage the implementation of the types of prevention measures that are in place in New York and that have been proposed by the FDA.

Another element is the surveillance capability and the prevention capability that goes with the public health function and with the prevention research function that allows us to gather the kind of information and that is so useful in following up on these kinds of problems and implementing very rapid responses to protect public health.

Senator CARPER. Do I understand that the FDA has developed regulations of its own for our country; is that correct?

Dr. SOLOMON. Certainly FDA has proposed a set of regulations and guidelines and I think we will be hearing about that later.

Senator CARPER. What is the timeline at FDA, do you know, in terms of accepting public comment, modifying the regs?

Dr. SOLOMON. I am not familiar with that. I am sorry.

Senator CARPER. Maybe we will find out later. Again, our thanks to both of you for being here. Thanks for your contributions.

Chairman COLLINS. I want to thank you both for your testimony and we will now turn to our third and final panel today. We have one witness, Dr. Jesse Goodman, who will be testifying on behalf of the Federal Food and Drug Administration. Dr. Goodman is the director of the FDA's Center for Biologics Evaluation and Research. He is also, I am told, a specialist in infectious disease and a practicing physician.

Dr. Goodman, before I have you give your testimony today I so want to acknowledge the fact that I believe you have only been in your current position since January, so obviously this is a problem that you inherited as opposed to created. But nevertheless, I hope you understand how frustrating it is for me personally and for those of us who have worked on this issue for years now, to find that we are no closer to final regulations, or virtually no closer than we were when I held a hearing on this issue 2 years ago. To hear the tragedy endured by the Lykins family I know moved you as well. So with that introduction, I would ask that you proceed with your statement.

TESTIMONY OF JESSE L. GOODMAN, M.D.,¹ DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. GOODMAN. Thanks very much, Madam Chairman, and Members of the Committee. Thank you for the opportunity to be here today on this important matter.

You really introduced me but just as you said, since January I have been director of the Center for Biologics at FDA, and I am also an infectious disease physician. So I am familiar with these problems and in fact have been involved in treatment of individuals who get infections after tissue transplants.

¹The prepared statement of Dr. Goodman with an attachment appears in the Appendix on page 61.

CBER, the Center for Biologics, is the FDA center that is responsible for regulating many types of human tissues and cells transplanted during medical procedures. We also have some other very important public health responsibilities in terms of blood, vaccines, and other novel therapies. I really do appreciate and share the concern of the Chairman and the Committee Members that we do everything we can in this area. Let me assure you that Commissioner McClellan and I are very committed, while new in our roles at FDA, to doing what we can to advance the field of tissue safety.

Also I really want to convey to the family and friends of Brian Lykins how sorry I certainly am for their loss. As a father, I can only begin to imagine how this has affected them. Again, while there is nothing that I can say here that will take that away, I do want them to understand the high level of commitment we have to do what we can to prevent problems like this in the future.

In my testimony I am going to briefly provide some background on human tissues and their use, discuss some of the safety concerns and their evolution, and in fairness, describe some actions that we have already taken under existing regulations as well as the actions we plan to take to enhance tissue safety.

Transplanted human tissue products have the potential to treat or cure a wide variety of health conditions. Over the past decade, advancing technology has expanded the therapeutic uses of tissue-based products. As we heard from Senator Collins, it is estimated that over 800,000 tissue transplants will be performed this year and, fortunately, the vast majority of these have very positive outcomes. In fact these products have dramatically increased patients' quality of life in ways that were previously unheard of. Senator Pryor's experience is a positive example and we would like to see everyone have that experience and certainly that is what we are working towards.

Cells and tissue have new uses. They can also be used in combinations with drugs or devices for doing things like delivering gene therapies. So there is a lot of promise here, and there is a potential to provide treatment for diseases as diverse as cancer, Parkinson's disease, even diabetes and other serious conditions.

However, with the increased uses of human tissues has come a heightened public awareness of the need for appropriate regulations. During the 1980's there were reports of multiple incidents of transmission of the chronic neurologic disease, Creutzfeld-Jakob disease by brain-covering allografts. A 1992 report documented seven HIV infections occurring from a single donor. And in the 1990's, possible transmission of Creutzfeld-Jakob disease through corneas and eye tissues was reported.

Now most recently, and this is very relevant to the tragic case we are hearing about today, it has become increasingly apparent that tissues are also subject to contamination from other agents like bacteria and fungi. These are unlike the viruses like hepatitis and HIV which come from donors who were not aware, or from a system that was not aware they carried a disease. These risks may have little to do with the donor. Rather, they may relate largely to how the tissue is handled, processed, and then tested.

As part of the FDA's efforts to address tissue safety, in December 1993 the agency published an interim rule for human tissue in-

tended for transplantation. This rule provided specific donor suitability and testing requirements for relevant human tissues. Like actions we had taken to improve blood safety, FDA was acting primarily to counter the transmission of HIV, hepatitis B, and hepatitis C. This rule also provided for the inspection of tissue banks and the recall and possible destruction of unsafe human tissue. In fact events that later occurred with CryoLife, as we will hear.

These efforts were part of our risk-based regulatory approach to tissues, recognizing the importance of these tissues and maximizing benefits while minimizing risks with the whole goal in the end being promoting public health.

Now I would like to report on eight areas of agency activities since the Committee's last hearing 2 years ago on this subject. These include many actions taken in response to the need to help better prevent the types of problems that led to Mr. Lykins' very tragic outcome.

First, the death of Brian Lykins and other reports of infections in recipients prompted collaborative investigations by FDA and CDC, as you have heard, and in some cases involving the State of New York. Extensive testing at CDC implicated CryoLife tissue in the fatal infection and other reported infections. This led to a comprehensive inspection of CryoLife, the tissue bank that processed the implanted tissue.

As an urgent response to these investigations, FDA also decided it was critical to take additional steps now, not to wait for regulations necessarily, to control the threat of bacterial and fungal contamination during manufacturing. In March 2002, we issued a guidance for immediate implementation concerning requirements for validating procedures for processing human tissues under existing regulations. This guidance and the accompanying outreach to industry and professionals emphasized important steps believed necessary to reduce the risk of contamination.

Second, our CryoLife inspection uncovered numerous and significant violations of FDA regulations. You have heard some of these today. When CryoLife failed to respond adequately to these deficiencies, FDA issued an order for retention, recall, and destruction of tissue in August 2002. This resulted in a recall of 7,913 tissue products. Further actions by FDA and CDC resulted in the firm committing to take appropriate steps necessary to ensure the safety of the tissues it supplies.

Third, the FDA, which had conducted—if we go back to the year 2000—we conducted 93 tissue establishment inspections then. We conducted 132 in 2001, increased that to 165 in 2002, and in fiscal year 2003 plans call for conducting over 200 inspections. I am pleased to be able to report that as a result of this activity, FDA has now inspected approximately 95 percent of the 162 registered tissue processors. By the end of fiscal year 2003, our Office of Regulatory Affairs plans to have completed inspections of 487 of the 512 registered tissue establishments. This includes not just processors but establishments that may test or ship or distribute or store tissue. Again, this is about 95 percent.

These increasing activities in recent years resulted in 2001 to 2002, for example, 99 investigator reports noting compliance deficiencies that warranted attention. We believe that these inspec-

tions and reports are already helping to increase awareness, correct deficiencies, and ensure that better practices are followed, including proper practices to prevent contamination such as we have heard about today.

Fourth, in October 2002, we created a new office, an Office of Cells, Tissues and Gene Therapies which coordinates regulatory and review activities for tissue products.

Fifth, the emerging challenges of chronic degenerative neurologic diseases such as CJD and variant CJD, or mad cow disease, prompted us to issue a draft guidance regarding appropriate donor deferral for donors.

Sixth, very related to this, on October 22, 2002 FDA issued a rule to classify human dura, which is brain lining, as a Class II device in order to establish controls to assure safety.

Seventh, In order to achieve a more robust surveillance system, FDA is continuing to work with CDC to stimulate adverse event reporting and to investigate reported events. CDC, as you have heard, has unique capabilities to conduct such surveillance. And we are working on our own and with CDC to obtain adverse event information, including from health care databases.

Eighth, working collaboratively with tissue manufacturers and trade and professional associations to identify new safety issues and improve tissue practices is also an important component. With this goal in mind, FDA has dramatically increased outreach activities in recent years in an effort to anticipate and avoid safety problems.

I should mention that this includes highly productive interactions with some of the professional associations, including the one Senator Collins mentioned, the American Association of Tissue Banks, as well as the eye banks and reproductive medicine associations. These associations have gone a long way through their voluntary programs to improving standards in their industry. Many companies, but not CryoLife, participate in those standards.

In addition to these activities, as you have alluded to, FDA advanced three regulatory proposals. The first rule established suitability determinations for donors of human cells and tissues. The second rule regards good manufacturing practices. And the third rule, which became final in January 2001 required the registration and listing of the tissue establishment. In fact this rule has already provided important information to direct and manage our risk-based inspection activities. It is a success, I think, of the publication of this rule that we have been able to really enhance the inspections and reach the 95 percent of targeted folks.

Under FDA's proposed regulations we would maintain this complete database of tissue products and establishments. We would provide more comprehensive detailed requirements designed under good tissue practices to help assure high quality during manufacturing, to further helping to prevent bacterial and fungal contamination.

We would require establishments to maintain complaint files and investigate complaints, and to report adverse events and product deviations to the FDA; issues that have been identified here. The proposed rules would establish tracking requirements to allow the agency to find recipients of implicated tissues if needed. The pro-

posed rule would also augment existing requirements for screening and testing of donors for relevant communicable diseases. This would also help us to rapidly respond to new infectious disease threats such as West Nile virus which is something we have been devoting a lot of energy to in our center.

While we have made substantial progress in this effort, the donor suitability and good tissue practice rules, as alluded to here, are continuing under review and discussion. Given that these regulations will create significant change, we want to be sure both that they are effective and that we achieve the proper balance of enhancing safety and quality while not causing undue burden or complexity that would inhibit the development or availability of products that benefit Americans. In fact we want these rules also to be flexible enough to permit the use of new and better technologies to do things like sterilize tissues or improve safety.

As you heard from some of the testimony, we want to be sure that as we do these rules we do not create a situation of shortages or non-availability of certain tissues that actually could hurt people if they needed the tissues. So we do want to get the right balance here.

We do believe that the extensive process of comment and input that has taken place will help us achieve these objectives. We are not sitting on this. We are actively engaged in moving forward. We have taken significant steps to make tissues safer than they were 2 years ago.

However, and even though they are rare, tragic adverse events like that of Brian Lykins—and as you said, it is not just an adverse event. This is something that really affects human beings. That is why I do this. Tragic events like this are devastating, and we are committed to doing what we can to prevent them. When a patient has a procedure involving a tissue product, we want to do our part to help make sure that patient can be as confident as possible that the product will be safe and free from any preventable risk of contamination.

I have been very active working to resolve remaining issues and I am committed to doing everything I can to help in this effort. I would be glad to answer any questions.

Chairman COLLINS. Thank you very much, Dr. Goodman. I guess what I was hoping to hear from you today was that the previous FDA officials blew it and that you were going to promise me that within a time certain we would have the regulations. I understand you might not want to comment on the actions of your predecessors, but I want to go through a bit of a timeline with you just so you can better understand the frustration that many of us are feeling on this issue.

The FDA's first regulation of tissue banks actually goes back to 1993. But it was in 1997 that the FDA started looking at the very issues that we are talking about today. In May 2001, 2 years ago almost to the day, I chaired the hearing at which your predecessor Dr. Zoon testified. She told me the FDA was committed to completing the regulations. I thought it was imminent at that point. There was testimony at that hearing that clearly said that the adequacy of tissue supply was not a concern, and indeed when you look at the number of transplants which has soared, some more

than 800,000 last year alone made available in the marketplace, I am not sympathetic to the argument that somehow the FDA regulations are going to cause shortages.

When I had the hearing, as I said, 2 years ago, I got a commitment from Dr. Zoon that the regulations would be issued. After repeated phone calls throughout the remainder of that year when nothing happened, I wrote in February 2002 to the FDA. I expressed my frustration, the agency was taking such an inordinate amount time to complete its work, because its work was good. It knew what to do. It had come up with a reasonable protocol. All we were asking was that it be made final, that it be made effective.

I asked when the regulations would be completed. The answer—actually, I wrote again. That was in December 2001, I wrote to the acting principal deputy commissioner. I did not even receive a reply to that letter. In February 2002, I again wrote to FDA. This time I received a reply 2 months later in April and the answer was, we do not know. We do not have a date for publication and implementation of the final rules. Again, this is 5 years later at that point.

In March 2002, we had a report from the CDC after Brian Lykins' death in November 2001 in which the CDC said, the findings in this report have important implications for patient safety and indicate that Federal regulations and industry standards on processing and quality control methods need to be enhanced and implemented. So here we have the CDC calling for implementation.

In October 2002, I asked Commissioner McClellan at his nomination hearing about this issue. Over and over again I have asked. I have written everyone I can think of. I have a stack of correspondence. We have called. When is this going to happen? The evidence is overwhelming that the FDA has come up with a good approach. We have examples in three States of effective regulation. So if there are some issues remaining, could we not look to the experience of those three States? When are we going to finalize these regulations?

Dr. GOODMAN. I share your concern and some of your frustration and I do appreciate it. When I started as center director, I know that within those first few weeks I said to staff, and when I was able to share it with Dr. McClellan, that I thought this issue and moving forward should be a very high priority. It is on my list of high priorities. It is not through lack of attention right now. I do not see a problem there.

There is a new commissioner. They are complex rules. We want to do it right. I personally feel that the framework which has evolved with a lot of outside input and discussion with folks like the tissue banks, with our colleagues at CDC and the States, with a lot of comments and input I think it is a good direction and deals with appropriate issues in a number of areas that I would like to see us deal with. So I am very committed to doing that. We are working, the new commissioner and I are working actively on that now and hope to resolve some of those issues.

For some of the reasons you have said and some of the past experience, I do not control the exact timeline and also would not want to give you one that is inaccurate. Also, I think that we want to come up with the right product, as I said here, to meet our common

goals, the goals to deal with some of these areas where we could have improved standards and regulation.

Chairman COLLINS. Dr. Goodman, I do not doubt your personal commitment and I do not doubt your sincerity, and I do not doubt your expertise at all. But we have to act. I cannot allow more Brian Lykins to die because we did not have regulations in place. Every expert with whom I have consulted has told me that they believe that had those regulations been in place and had CryoLife followed them, we would not have had the death of Brian Lykins. That is just so troubling to me.

Dr. GOODMAN. Right. I would like to respond to that because those are very important points. One is that we too want to do everything we can to prevent bad outcomes from medicines, medical procedures, and in this case from tissues. I agree with that totally.

What I do want to emphasize is that we are in agreement that there are areas where what can be done through regulation can be improved, and that some of those would help prevent problems like Brian Lykins' death. That is particularly what drives me and makes it important. I do not want to see more of that.

But what I also want to point out is that FDA's actions at CryoLife and in response to the investigation conducted in collaboration with CDC where under existing regulation we did show that in fact CryoLife was violating existing standards and rules. Our view is not just a guidance but they were violating principles that are there in our regulations and those are the basis of our activities.

Now, that said, there are ways in which elements of the proposed rules provide additional layers of protection and augment that existing authority in substantive and real ways that I think could add value to the public health process. Those are the things that I am committed to trying to move forward.

Chairman COLLINS. My time on this round has expired so I am going to yield to my colleague, Senator Pryor. But when we come back, I am going to direct to the deposition of CryoLife in which it said it did not have to report to the FDA of adverse events. It did not have to follow the regulations because they were just guidance and they were not effective, they were not in effect. I think that is very troubling and should be to you as well.

Dr. GOODMAN. I agree. We can discuss that, for sure.

Chairman COLLINS. Senator Pryor.

Senator PRYOR. Thank you, Madam Chairman. I must tell you, Dr. Goodman, I am not really satisfied with most of your answers today. The reason I am not is because, by and large, you have given us answers related to process, not action. I want to know what you are going to do to get these regs out.

Dr. GOODMAN. Again, I appreciate your concern. I am not somebody—sometimes we have processes that we need to assure we take the right action and to assure we get the action done.

Senator PRYOR. This has been pending at your agency for a long time.

Dr. GOODMAN. Right. I appreciate the frustration over that. As I said, in answer to your second question, I have engaged the commissioner and his office, I am working very diligently and deliberatively to resolve any issues so that we can move forward on the key

things here. So I agree with you on that. Without in any way diluting the importance of that work we need to do, I also would like to say that it has been very important to me looking at this issue even in the time since I have been center director to assure also and to let you know that under our existing authority we have not been doing nothing. We have dramatically gone out there and increased inspections.

The inspectors we have out there have been trained in procedures and issues related to exactly the kind of problems that led to this tragic outcome. As a result we are seeing, for instance, more voluntary recalls, more actions, and we believe that even our ongoing actions, which are contributing to improving quality and helping prevent such events.

Do they achieve all the things that would have been achieved under the proposed rules if they were finalized? No. For that reason your comment is very important and I acknowledge and share your interest in moving forward.

Senator PRYOR. What issues are left to be resolved at the agency before you get these out?

Dr. GOODMAN. Again, we have just recently briefed and engaged Dr. McClellan and staff, and the commissioner, who is new, and his staff in the commissioner's office, on these issues. There are quite a number of elements of these rules. It is not one single thing or another. We want to be sure we are placing the priorities in the right place, the things that will enhance patient safety while not causing undue burden, get the right balance here and move forward.

Senator PRYOR. But specifically, what obstacles are left within the agency to do that?

Dr. GOODMAN. I think the only obstacles are identifying issues where those kinds of concerns are and then resolving them in a way that can get us to the satisfactory end point. I think I do not have a specific list here. This process has been moving forward and quite a number of unresolved issues I think people have come up with solutions for them.

Senator PRYOR. Is there any reason why these regulations cannot be released in the next 90 days?

Dr. GOODMAN. I think that we at FDA—again, I understood Senator Collins' point of view too in terms of moving these forward. I think we do have some work to do on them. Again, I am going to work on those, and work with the commissioner on those within the next 90 days and try to do everything we can to move forward in a constructive way.

We are not, also, the only parties to this obviously. Everything we do is reviewed legally within the agency and the Department, and at a policy level in the Department. Now we are trying, and we plan to engage collaboratively in that process to make this more effective and move it forward. But I agree with you. We are going to do everything we can during the next 90 days to move things forward.

Senator PRYOR. Do you need any additional statutory authority to move forward?

Dr. GOODMAN. I am not aware at this time that statutory authority is at issue here. We feel under the Public Health Service Act,

in terms of protecting people from communicable diseases that we have authorities, and that the proposed rules largely build on those authorities. So we do feel we have the authority.

Senator PRYOR. I am interested in Senator Collins' questions here in a few moments about the deposition relating to CryoLife and I would really like to hear and delve into that and know what is said. But one question I have for you is, given the violations that CryoLife was engaged in, and I guess has admitted to at this point I guess, why are they still in business?

Dr. GOODMAN. I think that is a good question. What I would say is that FDA has taken a number of actions with respect to Cryo-Life. Included in those actions in terms of permitting them to continue to release tissue were a number of steps in an agreement reached with them. First of all, just let me say that as I mentioned, they were required by our action to recall a large number of their tissues and they entered into agreement with us to take the needed steps to assure better safety in their tissue processing.

Also during the interim period while they were taking these steps, a number of extra safeguards were put into place through this agreement including many of the things that CDC and Dr. Linden from the New York State Health Department alluded to. This includes the things we wanted to see valid, I say valid pre-processing culture of these materials, appropriate disposition of materials which failed, valid culturing of materials after processing, and again, appropriate disposition of material that failed, and a commitment to create and validate their own procedures to do this.

So there was quite a significant discussion and a substantive agreement reached in order to, what we felt was to ensure needed elements that a safety program was in place there and that overcame what we felt were, as I said, quite serious violations even of the existing standards.

Senator PRYOR. I am out of time. Thank you, Madam Chair.

Chairman COLLINS. If you need additional time, feel free to proceed.

Senator PRYOR. I was just going to ask with regard to CryoLife, as part of the agreement that the agency reached with this company, is there an ongoing monitoring to assure that the FDA has assurance that they are complying?

Dr. GOODMAN. Yes, there are ongoing inspections, there are meetings. So the answer is yes. We are still concerned. They have steps in the right direction, but these interim procedures are still in place in terms of the additional culturing and other procedures with their materials. But they have taken steps. Those steps are not finished, and we are going to watch this carefully as this goes forward. We are quite concerned about this.

Just getting back to the availability issue, this is one area where we did hear from a number of surgeons and others who use certain of their products for what they felt were essential and lifesaving issues. Part of what we did with CryoLife was make sure—this again addresses Senator Collins and the Lykins family comments. Part of what we did in CryoLife was work with them to be sure that users were also informed about some of these issues with their

products and could themselves help make an informed risk-benefit situation in the situation they are in.

Again, I think we have taken substantive action in this case. But again, as I said, I think some of the components of the proposed rules will, we hope, prevent and better deal with future situations like this.

Senator PRYOR. Madam Chairman, I will make this the last question. You mentioned a minute ago that you still have some concerns about CryoLife. They are taking some steps. They are not completely there yet. Yet the agency is allowing them to still be engaged in the business. Why not force them to clean it up first before they re-enter the business?

Dr. GOODMAN. There are two components to that. One is, because they have not completely finished all their progress on the various things in their agreement with the agency, they are taking additional steps that would not normally be required in terms of these outside cultures and oversight and agreements of what they will do in response to these cultures with us. So there are additional measures in place to provide assurance that these kinds of problems are dealt with. So that is the first component of that.

The second is just to state—and I do not want to equate these problems with all problems observed in all FDA inspections or whatever, but in most cases there are different kinds of levels of concerns and observations in different kinds of inspections, and very frequently when FDA makes observations of concerns like this a company will move quickly to correct those in a manner that gives us assurance that the product is safe and will remain safe. In this case some of those steps have been taken but not all, so there is a need to have additional steps in place.

Senator PRYOR. Thank you.

Chairman COLLINS. Thank you very much, Senator Pryor.

Dr. Goodman, CryoLife was well aware of problems related to infections of some of the tissue that it was providing long before Mr. Lykins died in November 2001. The corporation's internal reports reflect that in May 1998 the company received a report from a surgeon indicating that a patient had a problem with an allograft. Cultures indicated the growth of *Clostridium* bacterium. The patient then required the removal of the allograft due to continued problems with infection. In the year 2000 there were at least six complaints to CryoLife regarding bacterial infections. In 2001 there were 10 complaints at least regarding bacterial infection, and one of hepatitis C transmission from an allograft. I mentioned earlier that I have a list of 18 lawsuits that have been filed against the company as a result—each case involving tainted tissues.

Now the details of each of these complaints vary but there is clearly a pattern indicating a problem. There is one common notation made by a CryoLife employee on each of the complaint reports. I want to quote it to you. It says, "orthopedic allografts are not classified as medical devices as defined by FDA regulations and therefore are not reportable." So CryoLife was all too aware that the serious problems that had been reported by surgeons, and other health care providers to the company did not have to be reported under current FDA regulations.

Should it not be mandatory for tissue banks to report adverse events such as these to the FDA?

Dr. GOODMAN. I would like to see reporting of adverse events that the tissue banks and processors are aware of to the FDA. I think it could be helpful, as you allude to, in identifying problems ahead of time, and it is an element of the proposed rules. I agree with you.

I cannot comment on the motivation or anything like that, but you are right. And not just adverse events. It is important that another component of what has been proposed is that complaints are investigated and records kept of those complaints. So even if something is felt not by a company or a surgeon even not to be due to a graft or some other medical procedure, it is information that can be helpful to FDA who may have information from other companies, other sectors of industry to identifying a problem. It might not even be a problem at one company. It might be a problem with something being done elsewhere.

So we do feel this is information that is helpful. It has been helpful in helping make other kinds of medical products safe. So I share your desire that we have such information and that we get it in an effective way.

Chairman COLLINS. Again, I think that proposed requirement for mandatory reporting just makes good sense and needs to be put into effect. That is not a complicated requirement to put into effect.

Dr. GOODMAN. Frankly, I think a lot of the issues about complaints, etc., these are good quality practices that irregardless of the FDA any good company should be following. But I agree with you, we cannot always count on that.

Chairman COLLINS. After Brian Lykins died his family filed a lawsuit against CryoLife and during that process, as I alluded to earlier, an executive of the company was deposed. During his deposition he made reference to the fact that the FDA had not imposed final regulations regarding what industry practices should be, but instead had issued what he called only non-binding guidance. Does it trouble you to learn that a tissue bank like CryoLife, which clearly does not follow ideal practices, is citing the FDA's failure to issue regulations as a defense?

Dr. GOODMAN. Of course it troubles me. One comment I would make is it is not infrequent for firms under FDA investigation or with whom actions have been taken that a firm might not like, it is not uncommon for them to question those actions or question the authority for those actions. Everybody loves us.

Irrespective of those kinds of comments I would say that we believe or we would not have taken the recall action, that we have clear and strong legal authority to do that irregardless of their comments. I am disturbed by their comments and I want to do everything we can to be sure that people do not believe that and to, in the ways we need to, enhance our activities, but I do not buy that.

Chairman COLLINS. When FDA did its inspection and issued a form 483, FDA inspectors noted 12 objectionable conditions identified at CryoLife. CryoLife's written response to the FDA does challenge FDA's authority. When questioned about that in the deposition the executive said, "there was a guidance document issued.

They were not formal regulations. They were opinions, and they were not in effect at the time."

One of my frustrations is I do not want there to be any doubt about your authority. I do not want a bad actor to be able to tie the FDA up in court because you have not gone through the final steps of issuing all the regulations. We need to clear this up. We need to end any doubt about your authority. We need to have clear regulations in place, and I believe the FDA has the right approach.

It is interesting that in the 6 years that these proposals have been pending, it is not as if FDA has proposed changing them in any formal way. In fact the American Association of Tissue Banks, the American Red Cross have endorsed the regulations. We need to get on with the job.

Dr. GOODMAN. I hear you and I appreciate those comments. I appreciate all of them and I understand your concerns. I do want to emphasize that while CryoLife may have questioned our authority in this case, this authority is the interpretation of the chief counsel of the FDA and the actions of the FDA, and we do not think there is question about authority in this case. That does not in any way mean that many of the proposals in the proposed rules are not helpful, will not help industry do a better job, will not help FDA do a better job. That is what we want to aim for, Dr. McClellan and I, helping industry and the FDA do a better job to help make tissues safer. I agree with that.

Chairman COLLINS. Dr. Goodman, I do want to thank you for coming today. I appreciate the fact that you sat through the entire hearing so that you heard firsthand the Lykins family testimony which I am sure you will agree that the death of their son is such a tragedy. If by acting to implement these regulations the FDA can prevent future cases like Brian Lykins, or future cases of disease and infection, we need to help you get that job done. If there are obstacles I ask again for FDA to come to us. That was a request that Senator Durbin and I made 2 years ago. If there is some new statutory authority that you need, as Senator Pryor asked you about, or if there are more resources, come to us. But let us get the job done.

I hope I have from you today, or else I will not let you go, a commitment, a personal commitment to work with us to get these regulations, which I view as absolutely vital to public health, implemented without further delay.

Dr. GOODMAN. First of all, thank you. I am personally committed and will make a commitment to you to do everything that I can and is within my power, which is not, as you know, everything in the world. But I will do everything I can that is within my power to move this forward. This is a high priority to me.

I think as we look at the proposed rules and as I work with Dr. McClellan and the commissioner's office we really do want to identify for sure what are the key things that we can do and we need to do to help improve safety here and move those forward. So I am giving you my commitment that I am going to do everything I can to try to do that.

Chairman COLLINS. I thank you for that commitment and you can be assured that I am going to hold you to it. I know again that you have only been on the job for a short time, but working to-

gether I am convinced that we can make a difference in this area. Again, thank you for being with us this morning.

Dr. GOODMAN. Thank you.

Chairman COLLINS. Before adjourning the hearing, I also want to say a special thank you to the Lykins family. Steve, Leslie, and Tammy spent time with me in my office yesterday as well as having talked to the staff. I am so impressed and moved by their courage and their determination to make something good out of the very worst tragedy that any family could suffer through. I just want to publicly again thank them for their courage and for their commitment, and to assure them that we will continue to work on this important issue.

I also want to thank my staff for its hard work. I am optimistic today that we are going to move forward, but I felt that way exactly 2 years ago, so this is an issue we will continue to follow.

The hearing record will remain open for 15 days for the submission of questions or any additional materials. I want to thank my colleague, Senator Pryor for sharing his personal experience and for being here for this hearing. The Committee hearing is now adjourned.

[Whereupon, at 11:56 a.m., the Committee was adjourned.]

A P P E N D I X

The Lykins Family Statement

Steve

In September of 2001, our son Brian had orthoscopic surgery to remove a bone chip in his knee. It went very well. Afterwards, Dr. Mulawka, the surgeon, showed us pictures of Brian's knee, which revealed a quarter-sized divot in the bone. He told us that Brian should have follow-up surgery in order to prevent future arthritis in his knee. He also explained that a piece of bone from a cadaver would be used in the procedure and told us about the effort and testing that went into ensuring the donated bone tissue would be clean and safe. It was supposed to be a routine surgery, one that Brian could have lived a completely normal life without. In other words, it was a strictly a preventative and elective procedure. The recovery from the procedure was expected to take a little longer than the previous one, but no one expected any significant complications.

On Wednesday, November 7th, Brian had the follow-up surgery, which went well. Dr. Mulawka told us that Brian might become a little sick from the medications and possibly experience more pain than the previous surgery, but, otherwise, the recovery should go well.

After the operation, Brian was experiencing a lot of pain. He had a horrible headache, upset stomach and felt like he was burning up. The nurses, however, said his temperature was normal. The doctor decided to keep him overnight for observation. Leslie and I drove home to Willmar for the night.

We did not expect any complications, so I left for work the next morning and was scheduled to work in Minneapolis for the next five days.

Leslie

After Steve left, I drove to St. Cloud Hospital to pick up Brian. When I got there I found he was sick to his stomach and in excruciating pain. The pain pack the doctor had inserted into his knee during the operation wasn't working. The purpose of the pain pack was to administer medication directly to the knee to help control the pain.

After Brian was released from the hospital, I drove him to the St. Cloud Orthopedic Clinic where they removed the pain pack. Brian was originally scheduled to go to the doctor on Friday, the following day, but the doctor thought he could wait to see Brian until Monday morning. So, instead we drove to my home in Willmar where Brian stayed with me overnight. Throughout the evening Brian began to feel better. His knee was still sore and he felt warm at times, but otherwise felt fine.

On Friday morning, Brian woke up feeling much better. Of course, his knee was still sore, which was to be expected. That afternoon, he said he felt well enough to go home. At his home, he rested, ate and drank a bit, used the exercise machine and occasionally iced his knee. His recovery was going exactly as we thought it would. That evening, we watched a movie together and he told me that he felt fine and if I wanted to go home, I should, which I did.

On Saturday, I had previous plans to be out of the house most of the day, so I was up early. Brian called me, told me he felt fine, and asked some questions about when he was supposed to take his medication. He said his leg was still sore, but otherwise felt fine. I then went out, returned home at about 5 p.m. and called Brian. He told me he had been sick to his stomach for a while, which we had expected. I told him I would come over to his house after I took care of a few things, and he said that was fine. I got to his house about 6 p.m. As soon as I arrived, I realized that he was in worse shape than he had let on. He was throwing up and told me he almost passed out twice walking to the sink. He complained about feeling warm, but he did not feel warm to the touch.

I called Dr. Mulawka's office right away and got the answering service. They told me they would call the doctor and have him call me back. Shortly after, someone else from the clinic called. When I explained how Brian was feeling, he told me to change the dosage on one of the medications, which was the likely culprit of his stomach problems. Brian told me he would like to spend the night at my house; so, we packed up some of his things and started to drive to my house, which was only two and a half miles away.

On the way, Brian said he would like to stop at the hospital and have them check him out. We got to the emergency room about 8 p.m. When the nurse and doctor on duty examined Brian, they suspected that he was simply dehydrated and put him on an IV. I think they also gave him something in the IV to help settle his stomach. He still complained about "burning up" and stripped off his shirt and blankets, but he still did not register a fever. Brian also complained about his knee hurting but the nurse could not find any unusual swelling, redness or hot spots. A couple of times he doubled over with an upset stomach before the medication seemed to help him. The nurse and doctor thought he would feel better once he was more hydrated from the IV. His vital signs seemed to be okay. The doctor also ordered chest x-rays and had blood drawn. After that was done, Brian was back in his room and resting better. No one seemed alarmed about anything and they told us that he could go home soon. Brian finally appeared to be dosing off to sleep. I was tired and told the nurse that I would go out into the emergency waiting room to get some rest. At that point, it was about 1 a.m.

I was in the waiting room for about fifteen to twenty minutes when someone came in and told me to come right away. Brian had suddenly taken a turn for the worse. He had been moved to a larger room in the ER where several people

were anxiously working around him. He was awake. After a few minutes, a doctor told me that Brian's vital signs had changed all of a sudden and they were trying to find out what was wrong. Then the doctor asked me if there was anyone in town who I wanted to call to be with me. I began to worry. He told me that I should call my husband who, thankfully, was in Minneapolis and not on a trip. I called Steve and the doctor explained to him that he should come to hospital immediately, that things didn't look good for Brian. I hadn't expected any of this when I brought Brian to the hospital. We thought he was just dehydrated and nauseous from the strong medicine. The doctors were now planning to move him to the intensive care unit.

I made my way to the ICU when Brian was being wheeled into a room. The doctor was trying to ask Brian questions. He answered in short statements. We hadn't been in the room long when Brian had a convulsion. He sat straight up and gave a loud, long groan. I think that's when he went into a coma. The doctors and nurses got me out of the room and attended to Brian. Some time passed and a nurse came and got me and brought me back to Brian's room. I wasn't in there for long before he had another convulsion. It appeared as though he stopped breathing until the doctor put some sort of respirator on him. I was then led back to the waiting room.

Steve got the hospital about 4 a.m. The doctor filled him in on Brian's condition and told him that they weren't exactly sure what was happening, but that it was life threatening.

Steve

Brian was in a coma when I got to the hospital. His blood pressure had been at zero for several hours. All the organs in Brian's body were failing. His heart was the last organ to fail and at 6:21 a.m. on November 11th, our son died.

Shortly after Brian's death, we learned that the tissue put into his knee was infected with a deadly bacteria. This infected tissue was allowed to be implanted in Brian's knee due to several industry and government failures.

1. There were no federal guidelines for the automatic rejection of high-risk cadavers. The cadaver that supplied the tissue for Brian's operation should have been rejected for at least 2 reasons. First: He died due to suicide so the time of death was uncertain. Second: The body was allowed to remain un-refrigerated for at least 19 hours before tissue harvesting began.
2. Cryolife procedures for preparing the tissue to make it clean and safe were flawed.

The Center for Disease Control began an investigation into the cause of Brian's death because two other men from the same area died within about 1 week of each other after having routine knee surgery. One of the men had his surgery in the same hospital as Brian. The CDC found the other two men died from blood clots. They did not have cadaver tissue put into their bodies. Their knee operations were completely different from Brian's. However, due to the presence of the deadly bacteria found in Brian's body, the CDC continued with a lengthy investigation into the cause of our son's death.

Over the next 6 months I talked on a regular basis with Dr. Kainer from the CDC who was running the investigation. I could not believe the things that I was hearing about the tissue industry as a whole and Cryolife in particular. How could a medical industry in the United States of America be allowed to operate like this? A medical industry allowed to operate with little or no state and or federal regulation, how could this be? The FDA had known about the problems in this industry for years and for some reason was dragging its feet in bringing about the necessary regulations. The CDC had clearly defined the problems in this industry and the FDA would do nothing about it.

It became very clear at that point that the CDC had no power to bring about change in this industry and the FDA was not going to do its job. Cryolife was going to continue to operate in the unsafe manner that caused the death of our son. So at that time we decided to bring a lawsuit against Cryolife. The purpose of our suit was to bring about change in this company and this industry. Money was never the motivation for the suit; it was only the vehicle that would get people to pay attention. We did not sue Dr. Mulawka, and we did not sue the hospital. We only sued the people responsible for Brian's death because they would not fix the problems on their own. All we ever wanted was for the people involved in Brian's death to learn from what happened and fix the problems. It became clear that Cryolife and the FDA would not fix the problems without the lawsuit. Less than 30 days after we filed the suit, the FDA shut Cryolife down due to their unsafe practices. Unfortunately, there are still no federal regulations to prevent companies like Cryolife from operating in unsafe ways.

One and a half years after Brian's death, the FDA is still only proposing regulations for the tissue industry. Nothing has changed! The tissue industry can still operate anyway they want, with little or no federal regulations. What is taking the FDA so long? In our lawsuit, we listed seven areas of meaningful reforms that are needed in this industry.

1. REJECT HIGH RISK CADAVERS
 - o Diseased Cadavers i.e. cancer, meningitis
 - o Over 70 years old
 - o Cadavers un-refrigerated over 10 hours
 - o Suicide Cadavers
2. TESTING OF TISSUE WHEN CADAVER IS RECEIVED
3. STERILIZE TISSUE BEFORE DISTRIBUTION

4. DISCARD CADAVER IF ANY CONTAMINATION FOUND
5. MANDATORY REPORTING OF CONTAMINATION TO:
 - o Federal Agencies
 - o End User Doctor
6. CERTIFICATION OF CADAVER HARVESTING PERSONNEL
 - o Uniform Basic Qualifications
 - o Uniform Training
7. MANDATORY ANNUAL PROCEDURE/INVENTORY AUDIT

Had these reforms been in place at the time of Brian's operation, our son would not be dead and many other people would not be dealing with some very serious medical conditions. How much longer is it going to take the FDA to do its job and bring the tissue industry into the 21st century? This industry has been allowed to operate like something out of the Wild West for too long. Too many people have had their lives ruined and too many people have died. We need reforms and regulations in this industry now, not someday. There is no question that the tissue industry is necessary and important for the advancement of quality of life, however, there is no need for it to operate in such a dangerous manner.



Testimony
Before the Committee on Governmental Affairs
U.S. Senate

**CDC Response to Infections Related
to Human Tissue Transplantation**

Statement of
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National Center for Infectious Diseases
Centers for Disease Control and Prevention
Department of Health and Human Services



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Good morning, Madam Chairwoman and Members of the Committee. I am Dr. Steven L. Solomon, Acting Director of the Division of Healthcare Quality Promotion in the Centers for Disease Control and Prevention's (CDC) National Center for Infectious Diseases. Thank you for the opportunity to report to you on CDC's activities with regard to the problem of infections occurring in association with the surgical implantation of transplanted human tissue.

Introduction

An allograft is human tissue, which is recovered from cadavers and processed before being transplanted into another person. The most common type of allograft is bone. Tendons, skin, heart valves and corneas are other common types of human tissue allografts. Allografts may be life saving and can substantially improve the quality of life for many patients, reducing disability and restoring mobility or sight. The use of allografts has increased dramatically in recent years. In 1999, tissue banks in the United States distributed approximately 650,000 musculoskeletal allografts, compared with 350,000 in 1990.

As with any surgical procedure, the implantation of human tissue allografts may be associated with complications, including infections at the surgical site. Although rare, some of these infections are associated with bacterial contamination of the implanted allografts, a complication that can result in serious morbidity and death. The findings associated with CDC investigations of allograft-associated infections have important implications for patient safety. In collaboration with the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and other partners, CDC continues to investigate reports of infections and assess the need for possible changes in the processing and quality control methods for allografts as a means of

preventing allograft-associated infections.

As indicated, transplanted tissue is commonly obtained from cadaveric material. After recovery from a cadaver, allografts may be processed by either sterilization or aseptic processing without sterilization. In aseptic processing, careful handling ensures that no new organisms are introduced during the recovery of tissues from the cadavers.

Tissues may be treated with chemicals or antibiotics to minimize intrinsic contamination, that is, bacteria that contaminate these tissues following death, and prior to or during recovery of the tissues. Thus, the tissue is not sterilized—the processing is only intended to reduce intrinsic contamination and prevent further contamination of the tissue.

Sterile processing involves the use of aseptic techniques during the recovery of tissue followed by treatment of tissue to eliminate contamination with bacteria, and other microorganisms such as mycobacteria, viruses, fungi, and spores. Gamma irradiation and use of ethylene oxide were historically used to sterilize tissues for the presence of microorganisms. Gamma irradiation at high dosages affects the biomechanical properties of the tissue, rendering some tissues nonviable. Although ethylene oxide sterilization does not affect the biomechanical properties of the tendon, it is associated with other complications following transplantation, such as inflammation at the site of implantation. Because of these inherent problems with gamma irradiation and ethylene oxide, most transplanted tissues obtained from cadavers has been processed aseptically rather than sterilized. However, because of the small but finite risk of potentially life-threatening infection from such tissues, new tissue sterilization methods, such as low temperature chemical sterilization, have been developed.

CDC Investigations Summary

In November 2001, CDC began an investigation after receiving a report from the Minnesota Department of Health of a fatal case of infection with *Clostridium sordellii* bacteria in a patient in Minnesota who had recently received a bone-cartilage allograft. A few days after surgery, the patient developed pain in the knee that rapidly progressed to shock; the patient died the following day. The laboratory found *C. sordellii* bacteria in cultures of the patient's blood obtained prior to his death. Investigators at CDC contacted the tissue bank from which the transplanted allograft had been obtained, and the tissue bank provided CDC with samples of non-implanted tissues from the same cadaveric donor. CDC laboratories identified *C. sordellii* in some of these tissues. As a result, CDC concluded that the infection in the patient in Minnesota resulted from intrinsic bacterial contamination of the cadaveric cartilage tissue. CDC subsequently contacted the healthcare providers of all patients who already received transplanted allografts from this same donor to determine if other infections had occurred. CDC found that ten tissues had been transplanted into nine patients located in eight states. One of these patients developed an infection following the surgical procedure. The CDC/FDA investigation showed that intrinsic bacterial contamination was possible because the allografts in this case had been processed aseptically before being sent out from the tissue bank but not sterilized.

In June 2002, CDC was asked to assist in the investigation of an increased rate of post-operative surgical site infections in patients at an outpatient surgery facility in California. CDC determined that the increased rate of infection was associated with patients who underwent specific types of orthopedic procedures in which an allograft implantation was used. Although intrinsic contamination of allografts was not shown to be the only cause of the infections associated with this increased rate of infection, all of the infected

patients had received aseptically, as opposed to sterile, processed allografts—by far the most commonly used procedure. None of the patients who received autografts (transplants of the patient's own tissue) or allografts that had been steriley processed developed infection.

In addition to investigating infections associated with bacterial contamination of allografts, CDC has investigated reports of infections caused by fungi, parasites, and viruses following transplant of organs and tissues.

Investigations of non-bacterial contamination

Hepatitis C

In June 2002, a physician reported to the Oregon Department of Health Services a case of acute hepatitis C in a patient that had received a patellar tendon with bone allograft from a donor approximately 6 weeks before the onset of his illness. No detectable antibody to hepatitis C virus (anti-HCV) had been found in the donor's serum at the time of his death in October 2000. The ensuing investigation conducted by CDC and Oregon Department of Human Services confirmed that the donor, although antibody negative, was infected with hepatitis C virus (HCV) as determined by positive results of testing for HCV RNA and was the probable source of HCV infection in at least eight recipients of organs or tissues from this donor. Although transmission from anti-HCV negative tissue donors probably is rare, determining the frequency of transplantations from such donors and the risk for transmitting HCV to recipients will be useful for evaluating the benefits and limitations of additional prevention measures such as nucleic acid testing to detect HCV RNA among organ and tissue donors.

West Nile Virus

In August 2002, several recipients of organs from a common donor developed fever with mental status changes. CDC, FDA, the Georgia Department of Public Health, and the Florida Department of Health conducted an investigation. This cluster represents the first recognized transmission of West Nile virus by organ transplantation. Findings from this and concurrent investigations have prompted FDA guidance to the blood industry to reduce the risk of transmitting West Nile virus infection through transfusions. Additionally, FDA is working with the blood and medical diagnostics industry to speed development of West Nile virus screening tests. CDC has strongly encouraged clinicians to report West Nile virus-infected patients who develop symptoms within 4 weeks after receiving organ/tissue transplantation or blood transfusions, or within two weeks after donating blood, organ, or tissue. Prompt reporting of these cases will assist in withdrawal and retrieval of potentially infected tissues and blood products and will help define the epidemiology and clinical significance of West Nile virus-related transmission through transplanted organs and transfused blood.

Chagas Disease

On April 23, 2001, a physician notified CDC of an acute case of Chagas disease. Chagas disease is an infection caused by the parasite *Trypanosoma cruzi*. It is estimated that 16-18 million people are infected with this parasite. In parts of Latin America, of those infected, an estimated 50,000 die each year. Chagas disease following solid-organ transplantation has occurred in Latin America, where Chagas disease is endemic, but had not been reported previously in the United States. This investigation identified three cases in the United States of *T. cruzi* infection associated with transplantation of cadaveric organs from a single donor. The donor, who had previously resided in an area in which Chagas' disease is endemic, had antibodies to *T. cruzi*, which supported the conclusion that he had been infected with this parasite.

CDC and the scientific committees of the Organ Procurement and Transplantation Network/United Network for Organ Sharing, are reviewing what steps to take with regard to the feasibility of laboratory testing of potential organ donors for *T. cruzi* infection.

Prevention Measures

Prevention of infections from transplanted tissues and organs requires both careful screening of donors and careful adherence to specific guidelines for processing and quality control measures such as culturing tissues before processing. Ultimately, CDC believes that the best way to reduce the risk of transmission of infectious agents associated with tissue transplants is to develop new methods of sterilizing tissue that do not adversely affect the functioning of the tissue when transplanted into patients.

As noted previously, both sterilization methods commonly in use (ethylene oxide and gamma irradiation), although effective even against bacterial spores such as those found in the Minnesota case, have associated technical problems. Nonetheless, the potential risks associated with the transplantation of aseptically processed tissues suggest that existing sterilization technologies used for sterilizing allografts, such as gamma irradiation, or new technologies with increased effectiveness against bacterial spores should be considered whenever possible.

Every effort should be made to use suitable sterilization methods; however, if that is not possible, every effort should be made to minimize the risk of intrinsic bacterial infection. Recovered tissue should be cultured before suspension in antimicrobial solutions, and if bacteria commonly found in the human bowel are isolated, all tissue from that donor that cannot be sterilized should be discarded. Culture methods need to be validated to

ensure that residual antimicrobials in the treatment solution do not result in false negative culture results. Performing both destructive and swab cultures should be considered. Recommended time limits for tissue retrieval should be carefully followed, since the risk of intrinsic bacterial contamination increases the longer the delay between the donor's death and the recovery of the tissue for transplantation. After a tissue bank or tissue processor receives a report of potential allograft-associated infection, remaining tissue from that donor should not be released until it is determined that the allograft is not the source of infection. Tissue processors should promptly contact public health authorities and health-care providers of recipients of tissue from the same donor implicated in an allograft-associated infection. In these cases, a sample of non-implanted tissues from that donor that were processed using the same processing method as the implicated tissues should be cultured by an independent laboratory using a validated method.

Public Health System Responses

Other public health interventions that will greatly facilitate the prevention and control of infections associated with tissue and organ transplantation are enhanced surveillance and enhanced communication with clinicians.

As part of the Minnesota investigation, CDC, in collaboration with FDA, requested that cases of allograft-associated infections be reported to CDC through state and local health departments, in addition to reporting of such cases to FDA. As well, cases reported to FDA were shared with investigators at CDC and state health departments.

As of March 2003, CDC had received reports of 62 allograft-associated infections. Ninety-three percent of these infections were associated with musculoskeletal tissues.

Cases of infection were reported from 20 states and involved tissues that had been treated at 12 different tissue processors. One tissue processor was associated with 45% of all reported infections. These surveillance findings have been shared with the American Association of Tissue Banks, FDA, and others.

Public health surveillance is critical to our ability to improve patient safety by preventing post-surgical complications such as allograft-associated infections. We cannot investigate problems, identify their causes, and implement control measures if we have not detected them. CDC surveillance data come from state and local health departments, as well as directly from healthcare providers and from patients, particularly from patients when a cluster of cases is heavily covered in the media, as in this case.

Although both CDC and FDA do receive reports of post-surgical infections that may be associated with contaminated tissues and organs, both agencies are currently working to enhance their ability to capture this much-needed information. Most reports are received through passive surveillance, which relies on the ability of alert clinicians to recognize a particular problem and their awareness of their role in reporting it to the appropriate public health authority. Passive surveillance systems, while less costly, often provide incomplete information and fail to capture many cases that occur.

By contrast, active surveillance uses a variety of methods to maintain communication with potential reporting sources to increase the completeness and accuracy of surveillance information. Through CDC's ongoing partnership with FDA, and with the cooperation of the tissue banking industry, CDC has continued to receive reports of post surgical complications associated with allograft transplants, some of which appear to be consistent with allograft-associated infections. As indicated earlier, reporting of

allograft-associated infections increased significantly in the period following publication of the *Morbidity and Mortality Weekly Report* article describing the first case in Minnesota. The frequency of reports has declined in recent months; whether this is because fewer cases are occurring or because fewer cases are being reported is a question that can only be answered by active surveillance. CDC has had effective active surveillance systems for monitoring healthcare-associated infections for over thirty years, through systems such as the National Nosocomial Infections Surveillance System. However, these systems have been limited in scope due to the significant burden on reporting sites of maintaining highly standardized and labor-intense detection methods and being assiduous in the completeness of their reporting.

By making use of advances in information technology, CDC is developing a greatly enhanced healthcare-based surveillance system called the National Healthcare Safety Network (NHSN). The NHSN will integrate, expand and improve successful public health knowledge management systems that consist of data analysis, feedback of health care institution-specific data, and linkage of data with guidelines and educational materials for health care providers. By connecting clinicians and other healthcare professionals to FDA and CDC guidance, to information about specific syndromes, such as allograft-associated infections, and to public health authorities, this system is being designed to complement the reporting function and quickly provide prevention and response information to the user.

NHSN is being designed to be a principal means for hospitals and other healthcare-institutions to collect and manage and report patient safety information in collaboration with CDC, other federal agencies, and state and local public health authorities. The NHSN will be a fully integrated component of CDC's Public Health Information Network

and adhere to the standards of CDC's National Electronic Disease Surveillance System.

Conclusion

Addressing the problem of infections associated with blood, tissue and organ receipt is part of the larger problem of patient safety, requiring significant changes throughout all parts of the healthcare industry. Organizations involved in organ and tissue procurement, and suppliers and processors of tissues must put in place assiduously followed procedures to assure that any risks associated with tissue transplantations are greatly minimized if not eliminated. State and federal public health authorities must continue to enhance their ability to collect, analyze, interpret, and disseminate information about potential patient safety hazards due to biological products (including blood, tissue and organs), medical devices, and medical procedures. Clinicians and medical professionals must, with our help, increase their awareness of specific patient safety problems and fulfill their role in reporting such problems promptly to the appropriate authorities so that appropriate action can be taken. CDC, FDA, and other partners, as noted earlier, are actively engaged in ensuring that biological products, including tissue allografts, are as safe as possible.

The recent report by the Institute of Medicine (IOM) entitled, *Microbial Threats to Health: Emergence, Detection, and Response* recognized thirteen individual factors contributing to the emergence of microbial threats. These investigations highlight one of these factors identified by the IOM, "the role of advances in medical technologies, such as blood transfusion and organ transplants, [that] have created new pathways for the spread of certain infections."

Thank you very much for your attention. I will be happy to answer any questions you may have.

Testimony by

Jeanne V. Linden, M.D., M.P.H.

Director, Blood and Tissue Resources
Wadsworth Center
New York State Department of Health

Good morning, members of the Committee on Governmental Affairs. My name is Dr.

Jeanne Linden. I direct the New York State Department of Health's Blood and Tissue Resources Program. New York State has spearheaded development of many innovative programs and maintains active regulatory oversight in many important areas of public health. Since infected tissue poses the risk of pathogen transmission to recipients, oversight of tissue banking activities is an essential component of any comprehensive public health regulatory program. Known risks include transmission of human immunodeficiency virus, hepatitis B and C viruses, human T-lymphotropic virus type I, rabies, Creutzfeldt-Jakob disease, syphilis, *group B streptococcus*, and other sexually transmitted diseases such as gonorrhea, *Chlamydia*, *Mycoplasma*, *Trichomonas* and herpes. Bacterial infections in recipients of aseptically processed cadaveric tissues and infections with emerging agents, such as West Nile virus, are also of grave concern.

In New York State, regulation of tissue banks began with adoption of standards for hematopoietic stem cell banks in 1988, for semen banks in 1989, and for human milk banks in 1990. In 1991, a successful comprehensive tissue bank oversight program was developed and instituted. Comprehensive rules set standards for donor medical history assessment and evaluation of risk factors for disease transmission, laboratory testing, and record keeping to ensure the ability to track disposition of donated tissue from donor to recipient and vice versa. These standards were formulated based on the medical literature, consensus of experts in the field, and existing standards of professional organizations such as the American Association of Tissue Banks, the Eye Banks Association of America, and the American Society for Reproductive Medicine. Technical requirements are in place for all human tissues intended for transplantation, research, or education, including cardiovascular tissue, musculoskeletal tissue, skin tissue, and eye tissue.

Licensure requirements for tissue banks apply to all facilities that collect, process, store, distribute, and/or transplant tissue in New York State. At present, 736 tissue banks are licensed to operate in the state, including more than 130 facilities located outside the state. The attached table enumerates the various types of tissue banks licensed to operate in New York State.

Comprehensive tissue banks include cardiovascular and musculoskeletal tissue banks, skin banks, eye banks, semen banks, oocyte donation programs, bone marrow collection centers, umbilical cord blood banks, human milk banks, and nontransplant tissue banks. In New York State, facilities that use tissues clinically, including hospitals, ambulatory surgery centers and physicians' offices, are subject to tissue bank licensure, as well as specific administrative, record keeping, and quality assurance requirements. Errors and accidents detected after distribution of tissue, as well as adverse events, must be reported to the Wadsworth Center within seven calendar days of discovery, affording another mechanism for effective oversight. Licensed tissue transplantation facilities must report any adverse events in patients that might be linked to the tissue.

From the very inception of the New York licensure program, staff identified unacceptable practices in tissue banks. In one case, two semen bank operators were using only themselves as donors, but, through the use of fictitious names, led physicians and recipients to believe that more than a dozen donors were available through the program. Testing and record keeping at this bank were virtually nonexistent. Another reported incident concerned a hematopoietic stem cell bank that transplanted the wrong component -- the ABO-incompatible red cells that had been removed from the bone marrow, rather than the marrow itself. Had the marrow not been retrievable, the patient, who had already undergone ablative therapy, could have died as a result of a severely impaired immune system. One surgical bone bank lost the skull flap of an autologous donor. These cases demonstrate the crucial importance of thoroughly identifying

tissues used for transplantation.

The death of Brian Lykins in November 2001 brought the inherent risk of using aseptically processed allografts to national attention. This tragic event spurred an immediate investigation by the National Center for Infectious Diseases of the U.S. Centers for Disease Control and Prevention (CDC). In cooperation with state departments of health, the CDC was able to obtain non-transplanted tissues from the same cadaveric donor whose musculoskeletal tissue was transplanted into Mr. Lykins and identified the pathogen bacterium *Clostridium sordellii* in some of the tissues. Ten tissues had been transplanted into nine patients located in eight states. A second recipient of tissue from the implicated donor also developed an infection, but cultures for anaerobic bacteria, including *C. sordellii*, were negative. This patient fortunately responded to antibiotic treatment.

The CDC investigation determined that CryoLife, the tissue bank involved in these cases, routinely cultures allograft tissues following suspension in an antimicrobial solution. Such a culturing protocol may lead to false negative results because of the bacteriostatic nature of certain bacteria, particularly spore-forming anaerobes like *Clostridium*.

In February 2002, absent its own jurisdiction or assistance any from other federal agencies, CDC asked the New York State Department of Health's assistance in obtaining records and seeking additional tissue samples from the donor implicated in the Lykins case that remained in CryoLife's inventory, as well as records and tissues from donors implicated in other allograft-associated *Clostridium* infection cases. The enforcement authority of the New York State Commissioner of Health enabled Blood and Tissue Resources Program surveyors to conduct an onsite inspection of the tissue bank, where several deficiencies were noted, including the failure to perform recovery culture testing. The Wadsworth Center, the Department's public health laboratory, isolated *Clostridium septicum* in tissues from two donors

implicated in allograft-associated *Clostridium* infections.

The Department also assisted CDC in identifying potential additional cases of post-transplant allograft infections by contacting physicians who had used tissue from implicated donors for transplantation. Since we were not able to share patient names with CDC because of patient confidentiality restrictions, we contacted the physicians involved directly.

The number of allograft-associated *Clostridium* infections per one million population was found to be significantly lower in New York State, compared to the remainder of the country (0 vs. 0.06, p=0.0009). CryoLife maintained two inventories of tissue for release: one for New York patients and a second one for patients in other states. Tissues from only two of the implicated donors would have met the requirements for tissue in the New York inventory; tissue from six of the donors would have been disqualified for distribution to New York. This likely contributed to explaining why there were no known cases of allograft-associated *Clostridium* infections in New York. We believe that New York State regulations have played a significant role in protecting the state's patients from such adverse transplant-related outcomes.

Based on our experience, we believe that a mechanism to ensure documentation of disposition of all tissues must be established and enforced so that donors may be traced in cases of adverse events, and all recipient outcomes reviewed and followed up as necessary. The 1985 LifeNet incident, in which numerous tissues were distributed from a donor in the window period of HIV infection, illustrates the need for accurate accounting of all allografts distributed by a tissue bank and issued for transplant by the hospital. In this case, six of 54 distributed tissues could not be accounted for by the transplanting hospitals. New York State's rigorous requirements for licensure and record keeping by tissue transplantation facilities are aimed to ensure accurate tracking of tissue to each recipient.

States that operate tissue bank oversight programs complement federal efforts in this

most important public health area. New York State established a partnership agreement in place with the Food and Drug Administration's New York District to share inspection documents and reports, and minimize duplicated effort.

We commend your endeavors to address this critical public health concern. While tissue banking is clearly in need of federal oversight and uniform minimum standards, any potentially deleterious effects of imposing overly restrictive standards on the tissue supply must be balanced against the proven benefits of such standards to the public health. Specifically, it is unrealistic to expect tissue banks to be able to guarantee the absence of contamination in a donor when tissues are processed aseptically (not microbially inactivated). It must be acknowledged that since some tissues are in short supply, patients' health could be adversely affected if potentially draconian regulations diminish that tissue supply.

The Food and Drug Administration's existing rules for tissue banks and progression toward current good tissue practices represent a valuable step toward enhancing tissue bank oversight nationwide. The established benefits of standards and oversight in this area are abundantly clear. The New York State program has identified several cases in which unsuitable donors have been rejected and recipients thus protected by adherence to the State's rigorous standards. However, any regulatory scheme developed must remain flexible enough to adapt quickly to escalating changes in this field.

Thank you for this opportunity to comment on this area of vital public health significance.

**NEW YORK STATE DEPARTMENT OF HEALTH
WADSWORTH CENTER**

Blood and Tissue Resources Program

Tissue Banks Licensure by Category

Type of Tissue Bank	Number of Licenses		
	In-State	Out-of-State	Total
Comprehensive Tissue Banks	117	103	220
Eye Banks	6	17	23
Reproductive Tissue Banks	44	22	66
<i>Semen only</i>	12	17	29
<i>Oocytes/embryos only</i>	3	0	3
<i>Semen and oocytes/embryos</i>	29	5	34
Hematopoietic Stem Cell Banks	35	16	51
Human Milk Banks	1	1	2
Other (Musculoskeletal, Cardiovascular and Skin Banks)	31*	47	78
Limited Tissue Procurement Services	10	3	13
Transplantation Facilities	268	0	268
Tissue Storage Facilities	3	18	21
Insemination Sites	171	0	171
Nontransplant Anatomic Banks	64	13	77
Total**	604	132	736

* Includes 17 "autologous" tissue banks

** Categories are not mutually exclusive; therefore, totals are not additive.

May 9, 2003



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STATEMENT OF

JESSE L. GOODMAN, M.D., M.P.H.

**DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND
RESEARCH**

**"TISSUE BANKS: THE DANGERS OF TAINTED TISSUES
AND THE NEED FOR FEDERAL REGULATION"**

BEFORE THE

COMMITTEE ON GOVERNMENTAL AFFAIRS

UNITED STATES SENATE

May 14, 2003

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Good morning Madam Chairman and Members of the Committee. Thank you for inviting the Food and Drug Administration (FDA or the Agency) to participate in this hearing on human tissue. I am Dr. Jesse L. Goodman, and since January 2003, I have been the Director of the Food and Drug Administration's (FDA or the Agency) Center for Biologics Evaluation and Research (CBER). I am also a practicing physician and a researcher specializing in infectious diseases.

CBER is the FDA Center responsible for regulating many different types of human tissue and cells transplanted during various types of medical procedures. CBER also regulates blood, vaccines, and many other therapies.

I specifically mention blood because, although the challenges it presents are different from tissue, there are nonetheless similarities in terms of the risks of infectious disease transmission associated with these products. Some of the same approaches that have been used successfully to improve the safety of blood are also being used to make tissue safer. Examples include donor suitability, performing appropriate testing, assuring that materials are processed and shipped properly, and monitoring adverse events.

Tissues derived from humans present unique challenges. The risks of transmitting infection can be significantly reduced, but not completely eliminated. While we constantly strive to increase the safety of blood, tissue and other products that we regulate, no medical product or procedure

is one hundred percent safe. Education, training and appropriate regulation are important measures we employ to help reduce risk.

I want to thank the Chair and members of this committee for your continued interest in a topic that affects the lives of so many people. I also want to convey to the family and friends of Bryan Lykins just how sorry I am for their loss. I know there is nothing I can say today that will ease their pain, but I do want them to know that my colleagues and I at FDA are committed to making tissue transplants as safe as possible prevent such tragedies in the future.

BACKGROUND

The term "tissue" covers many products transplanted for medical uses, such as skin replacement following severe burns, tendons and ligaments to repair injuries, bone replacement, and corneas to restore eyesight. Tissue transplantation is a rapidly growing industry. The number of musculoskeletal tissue transplants increased from approximately 350,000 in 1990, to more than 800,000 in 2002.

Transplanted human tissue products have the potential to treat or cure a wide variety of health conditions. Over the past decade, advancing technology and improved techniques have expanded the therapeutic uses of tissue-based products. For example, we have seen significant advances in tissues to treat severe burn victims. These products have dramatically increased patients' quality of life in ways that were previously unheard of. In addition to their important uses to restore and improve a variety of functions, these new techniques also hold the potential to provide therapies for diseases such as cancer, Parkinson's disease, hemophilia, anemia, diabetes,

and other serious conditions. Cells and tissues can also be used in combination with drugs or devices, and to deliver genes for gene therapies.

Many cellular and tissue products are regulated by FDA as biological products under both the licensing provisions of the Public Health Service (PHS) Act and the Federal Food, Drug, and Cosmetic (FD&C) Act. Several categories of human tissue used for transplantation are regulated as medical devices under the 1976 Medical Devices Amendments, including heart valves, dura mater (the brain covering) and some demineralized bone products. Most human tissues for transplantation, as defined in Title 21, of the *Code of Federal Regulations* (CFR) Part 1270, are regulated under the Agency's authority to prevent the transmission of communicable disease, section 361 of the PHS Act.

FDA has three primary goals with respect to human tissues: (1) to prevent the spread of communicable diseases; (2) to ensure that safety and efficacy is demonstrated for cellular and tissue-based products that are also drug, biological, and medical device products; and (3) to help enhance public confidence in these products so that, where appropriate, they can fulfill their great potential for saving and improving lives. We seek to accomplish these goals in a manner that will not discourage the development of new products.

With the increased use of human tissue has come a heightened need to ensure greater tissue safety and minimize the potential risks. Developments in the 1980s and 1990s prompted FDA to examine its approach to tissue safety. Several incidents illustrate the risks of infectious disease transmission when adequate precautions are not taken. During the 1980s, there were reports of multiple incidents of transmission of the degenerative neurologic disorder, Creutzfeld-

Jakob Disease (CJD), by dura mater allografts. A 1992 report documented that seven people were infected with HIV through transplantation of organs and tissue from a single donor. In the 1990s, possible transmission of CJD through corneas and eye tissue was reported and in 1999 a patient died from cardiac arrest during surgery to remove an infected corneal transplant. The probable source of the infection was contamination of the media used to store the cornea. Just last year, despite donor testing, there were three confirmed organ recipients and six probable tissue recipients who were determined to be infected by hepatitis C from a single donor's tissues. Tissues are also subject to contamination from other agents such as bacteria and fungi. These risks may have little to do with the donor; rather, they may relate to how the tissue is handled, processed and tested.

The overall risk of disease transmission through tissue transplantation is believed to be very low. However, more tissue transplants are taking place each year. Over 800,000 tissue transplants occurred in the past year. The public expectation for tissue safety is high and, as a result, FDA is taking steps to better understand, detect, prevent, and act upon threats to tissue safety.

As part of FDA's efforts to address tissue safety, in December 1993, the Agency published an interim rule for Human Tissue Intended for Transplantation (21 CFR Part 1270). This rule provided specific donor suitability and testing requirements for human tissues, including bones, musculoskeletal, skin, and ocular tissue. Like our actions to achieve blood safety, FDA was acting swiftly to counter the transmission of three serious disease agents: HIV, hepatitis B and hepatitis C. This rule also provided for the inspection of tissue banks and the recall and possible destruction of unsafe human tissue. When the final rule was published on July 29, 1997, a

guidance document on donor screening and testing was published to accompany and update the rule.

When the Agency put the 1997 tissue rule and guidance in place, FDA developed a plan to address tissues in a more comprehensive, but not unduly burdensome manner. The goal of this plan was to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new or existing products. We believe this will lead to safer and more efficient development of human cells, tissues, and cellular and tissue-based products, while increasing public confidence in those products. We designed our risk-based regulatory approach to tissues recognizing the importance of life-saving and life-improving tissues. This risk-based approach is intended to promote tissue safety in a manner intended to maximize benefits while minimizing risks.

RECENT DEVELOPMENTS

As you know, on May 24, 2001, my predecessor appeared before this committee at a hearing on the practices of the tissue bank industry. Let me report on Agency activities since that hearing in eight major areas, some of which are in response to FDA and CDC investigations into Mr. Lykins' case.

1. Bacterial Contamination and FDA Guidance on Validation of Procedures for Processing Human Tissues

The death of Brian Lykins and other reports of infections in recipients prompted investigations by FDA and CDC. Extensive testing at CDC implicated CryoLife tissue in

the fatal infection and other reported infections. This led to a comprehensive inspection of CryoLife, Inc. (CryoLife), the tissue bank that processed the implanted tissue.

As an urgent response to these investigations, FDA decided that it was critical to take additional steps to control the threat of bacterial and fungal contamination during tissue manufacturing. Therefore in March 2003, FDA issued guidance for immediate implementation concerning the validation of procedures for processing human tissues. This guidance and the accompanying outreach to industry and professionals emphasized the important steps that we believe are necessary to reduce contamination risks. We believed that it was important that all of the tissue industry, and not just a single company, enhance their procedures to avoid the problems experienced at CryoLife.

2. Continuing CryoLife Investigation and Recall

The ongoing CryoLife inspection uncovered numerous, significant violations of FDA regulations. When CryoLife failed to respond adequately to the deficiencies noted during the inspection, FDA issued a Warning Letter to the firm. Again, the firm did not commit to all of the corrective actions FDA believed were necessary. On July 15, 2002, CDC informed FDA that it had received 54 reports of allograft-associated infections, almost half of which were associated with CryoLife implants. In response, FDA issued an Order for Retention, Recall, and Destruction to the firm on August 13, 2002. The order resulted in the recall of 7,913 tissue products. Further actions by FDA and CDC resulted in the firm committing to take the appropriate steps necessary to ensure the safety of the tissue it supplies. Under the Order, on September 5, 2002, FDA and CryoLife entered into an agreement designed to ensure that tissue the firm distributes would be free of contamination. The most recent

inspection of CryoLife was performed in early February 2003. Some improvements were noted, but significant work lies ahead. FDA continues to monitor the firm and to work with the company as corrective actions are implemented.

3. Inspections, Field Training and Enforcement Activities

A lynchpin for assuring the safety of tissues is assuring that tissue manufacturers and distributors are handling tissue appropriately and using validated procedures to prevent contamination. FDA inspectors, organized under the Office of Regulatory Affairs (ORA), are the Agency's eyes and ears for assuring that proper procedures are in place and are being followed. Where appropriate, information from FDA inspections can and will be used to take enforcement action. However, it is preferable, wherever possible, to work with manufacturers to build quality into their procedures in an effort to prevent safety problems.

Working closely with ORA, we have upgraded and expanded our inspection activities. In fiscal year (FY) 2002, FDA held two extensive training sessions for the district investigators who perform tissue establishment inspections. Over 80 investigators were provided with detailed information on current and pending tissue regulations. To encourage consistent and effective inspections, FDA also published an updated compliance program guide in March of 2003, to assist our investigators and tissue establishments understand what will be addressed in a tissue establishment inspection. Training sessions for investigators are also planned for FY 2003 and FY 2004.

In FY 2001, FDA conducted 132 tissue establishment inspections, of which 51 resulted in the issuance of an FDA Form 483 report listing observations by an inspector of compliance

deficiencies or violations. In FY 2002, FDA conducted 165 inspections, and 48 of these resulted in the issuance of a Form 483 report. FDA plans to conduct over 200 inspections in FY 2003. These activities have resulted in 10 regulatory actions, including a mandatory recall order (CryoLife). There has also been an increase in recall activity, and most significantly the number of Class I recalls where there is a reasonable probability of serious adverse health consequences for recipients. In FY 2002 there were 10 Class I recalls compared to only one in FY 2000.

4. FDA Creates New Office

In October 2002, FDA created the Office of Cellular, Tissue, and Gene Therapies (OCTGT) to consolidate regulatory and review activities for tissues, cellular and tissue-based products, gene therapies, and xenotransplantation products. This office includes experts in molecular and cell biology, viral and nonviral gene therapy vectors, nucleic acid chemistry and genomics, proteomics, developmental and reproductive biology, stem cell biology and physiology, tissue and organ regeneration and medical and pharmacology/toxicology. OCTGT evaluates potential shortages to help assure the continued safe supply of needed products. This office works with CDC, NIH and other appropriate organizations to develop standards and methods for cellular therapies and participates in inter-center focus groups for collaborative reviews. Through this centralization of activity and expertise, FDA is working more effectively with our agency partners, conducting outreach, and regulating tissue products to achieve a safe and adequate supply.

5. Updating Donor Deferral Criteria to Respond to New Threats

In addition to laboratory testing, a critical component of enhancing the safety of tissues is excluding donors who may pose a higher risk of transmission of infectious diseases. The emerging challenges of prion diseases [such as CJD and variant CJD (vCJD)], for which there currently are no practical laboratory tests, pose a particular challenge, especially for nervous system tissues. Because of our concern about the potential transmission of these diseases by transplantation, implantation, infusion, or transfer of human cells, tissues and cellular, and tissue-based products (HCT/Ps), FDA issued guidance on June 14, 2002, regarding deferral criteria for donors potentially at risk of developing and transmitting these diseases. We published this draft guidance to present our current thinking about preventing the potential transmission of this disease by deferring donors with possible exposure. FDA intends to issue another draft guidance document for public comment that would include recommendations to screen and test donors for relevant communicable diseases other than CJD and vCJD, and combining both draft guidance documents into one final guidance of that time.

6. Dura Mater Proposed Rule

On October 22, 2002, FDA's Center for Devices and Radiological Health (CDRH) published a proposed rule to classify human dura mater as a Class II device. Class II means we know enough about the device category to establish controls for reasonable assurance of safety and effectiveness. A draft guidance document was published on the same day to support the proposed classification. The 90-day comment period for the proposed rule and the draft guidance document ended on January 21, 2003. The comments are currently under review.

7. Collaboration with CDC and Others

As I have discussed, incidents of infectious disease transmission by human tissue are not routinely reported. Current regulations do not require facilities to report incidents to FDA's MedWatch system, though voluntary reporting sometimes occurs. To date, only a limited number of adverse events relating to tissue have been reported to MedWatch. In order to achieve a more robust surveillance system, FDA is working with CDC to stimulate adverse event reporting and to investigate reported events. CDC has unique capabilities to conduct such surveillance and FDA is exploring ways to obtain adverse event information from CDC, as well as other health care delivery databases.

8. Training, Meetings and Outreach Activities

Working collaboratively with tissue manufacturers to identify new safety issues and improve tissue practices is critical to the success of our mission. With this goal in mind, FDA has dramatically increased outreach activities in recent years in an effort to anticipate and avoid safety problems. An addendum is attached to this testimony that describes the training, meetings, and outreach activities that FDA has conducted with tissue establishments, inspectors and professional organizations.

ENHANCED TISSUE SAFETY

FDA is committed to protecting public health by promoting greater safety of tissues used in transplantation. Greater assurance of safety in transplanted tissue will also be critical to public acceptance of this technology. The recent reports of serious bacterial contamination in tissues and West Nile Virus transmitted through blood and organ donors underscore the need for a

strong infrastructure to prevent and respond to new threats of tissue safety. In addition to the activities I have just described, FDA has advanced three regulatory proposals.

The first rule, proposed on September 30, 1999, would establish suitability determinations for donors of human cellular and tissue-based products. The second rule, proposed on January 8, 2001, would require manufacturers to follow current good tissue practices (GTP). The third rule, which became final on January 19, 2001, requires the registration and listing of tissue establishments.

FDA's regulations could enhance prevention and response in several ways:

- For the first time, a complete database of human cell, tissue, and cellular and tissue-based product establishments and products would be maintained. This would significantly increase the efficiency of FDA inspection and monitoring, and the effectiveness of communication about risks and related findings.
- Our proposed GTP rule would provide more comprehensive, detailed requirements designed to prevent bacterial and fungal contamination of tissues through appropriate manufacturing methods, facilities, and controls to enhance industry compliance.
- To prevent injuries and deaths, tissue manufacturers and FDA must identify, and rapidly respond to adverse events, particularly tissue contamination.
- Tracking requirements would make it possible for the Agency to quickly find recipients of implicated tissue. This would help ensure that when a risk is identified a timely and appropriate response can proceed.

- Requirements to screen and test donors for “relevant communicable diseases” would facilitate rapid implementation of new tests to detect emerging disease threats. This would enable us to rapidly respond to new infectious disease threats such as West Nile Virus as they emerge and as interventions become available to reduce risk.

FDA is committed to assuring the safety of tissues, and we are continuing to move forward to accomplish that goal. We also want to acknowledge the American Association of Tissue Banks (AATB) and other professional organizations for their work in publishing standards for tissue banks and advancing the safety of tissue transplants.

CONCLUSION

Hundreds of thousands of tissue transplants occur annually. Most of these are successful and free of adverse events. The future of tissue and tissue-based technology is promising. However, tragic events such as Mr. Lykin’s death indicate that we must continue to do more. FDA will continue to improve tissue safety and refine our approach as new technologies and products become available. In addition to the proposed regulations, we have significantly increased inspections, oversight and outreach, even as we advance new regulations. The Agency continues to hold workshops and public meetings on issues affecting human cellular and tissue products to identify the need for guidance and to promote regulatory compliance in order to facilitate the development and availability of safe tissue products. FDA is committed to preventing the transmission of communicable diseases to ensure the safety and effectiveness of cellular and tissue-based biological and medical device products. When a patient has a

procedure involving a tissue product, we want to do our part to make sure that patient can be as confident as possible that the product will be as safe and free from any preventable risk of contamination.

Commissioner McClellan, my staff, and I look forward to working with the Committee both now and in the future to address tissue safety and ensure the Agency is taking all needed steps to prevent injuries and illnesses associated with contamination of tissues. I will be glad to answer any questions.

ADDENDUM**OUTREACH / WORKSHOPS / MEETINGS****Publications:**

- Wells MA, "FDA Proposed Oversight of Human Reproductive Cells and Tissues used in ART, American Infertility Assoc. – In-Focus, Spring 2002
- Lazarus EF: Adoptive immunotherapy, the Food and Drug Administration and you: a regulatory approach to donor lymphocytes. *Cytotherapy* 4:5, 449-449, 2002
- Lazarus EF, Browning J, Norman J. et al: Sustained decreases in platelet count associated with multiple, regular plateletpheresis donations. *Transfusion* 41, 756-761, 2001
- Lazarus, EF and Klein HG: Apheresis, In Rich RR, Fleisher TA, Shearer WT et al (eds): *Clinical Immunology*, 2nd Ed. Harcourt Publishers, London, 2001
- Solomon RR, contributing author to: Lanza R, Langer R, Vacanti J (ed) *Principles of Tissue Engineering*, 2nd Edition. Chapter 65 – “Regulatory Considerations,” KB Hellman, RR Solomon, C Gaffey, CN Durfor, JG Bishop, Academic Press, San Diego. 2000
- Lazarus EF and Klein HG: Hemapheresis and cellular therapy. In Hoffman R, Benz EJ, Shattil SJ et al (eds): *Hematology: Basic Principles and Practice*, 3rd Ed. Churchill Livingstone, New York, 2000
- Wells MA – “Overview of FDA Regulation of Human Cellular and Tissue-Based Products,” *Food and Drug Law Journal*, Volume 52, No.4, October 1997
- Wells MA, “The Regulatory Reach of FDA: A Novel Plan,” *Regulatory Affairs Focus*, Volume 2, Issue 9, September 1997

General/Ongoing Interactions with Industry:

- FDA presentations/participation at American Association of Tissue Banks (AATB) and Eye Bank Association of America (EBAA) Annual and Mid-year Meetings
- FDA presentations/participation at AATB Reproductive Tissue Council Meetings
- FDA presentations/participation at Food and Drug Law Institute (FDLI) and Regulatory Affairs Professional Society (RAPS) meetings

- FDA presentations/participation at American Society for Reproductive Medicine (ASRM) annual meetings
- FDA site visits to tissue establishments
- FDA consultant to the CDC/Industry Task Group developing the model certification program for embryo laboratories under the 1992 Fertility Success Rate and Certification Act
- FDA liaisons to ASRM's, National Coalition for Oversight of Assisted Reproductive Technologies (NCOART)
- FDA liaisons to AATB Standards and Medical Advisory Committees
- FDA liaisons to EBAA Medical Standards Committee
- FDA liaison to American Association of Blood Banks (AABB) committee for Hematopoietic Progenitor Cell Standards
- FDA liaison to AABB committee for Umbilical Cord Blood Standards
- FDA liaison to AABB committee for Cell Therapy Standards
- FDA liaison to joint professional organization work group for drafting Hematopoietic Progenitor Cell Product Circular of Information
- FDA liaison to NCCLS immune cell functional assay work group

Meetings within the HHS/FDA:

4/17/03	Biologics Cadre conference call
4/9/03	HHS Advisory Committee on Organ Transplantation (ACOT) Working Group

Meetings with other Federal/State Agencies:

2003	Multiple meetings with CDC re: SARS
2002-2003	Meetings with HRSA re: Vaccinia
2002	Multiple meetings with CDC and HRSA re: WNV
5/03	Federal Interagency Work Group on Hematopoietic Stem Cells
5/03	Meeting with WHO regarding cell and tissue regulation
3/01	Meeting with Health Canada, Rockville, MD, to discuss the Regulation of Human and Xeno tissues
6/98	Meeting with Japan Health Science Foundation
1998-2002	Multiple meetings of the DHHS Interagency Task Force on Assisted Reproductive Technology (FDA, DHHS, CDC, CMS)

1998 issues	CDC - Multiple meetings on coordination of reproductive tissue
1997	Trilateral meeting between US, Canada, Mexico- Mexico City
9/97	HRSA - Discussion of regulation of pancreatic islet tissue
9/97	New York State Dept. of Health - Meeting with Dr. J. Linden on coordination of Tissue Bank Inspections
7/97	Federal Trade Commission - Discussion of Stem Cell Promotion

Specific Events with Industry:

4/26/03	FDA invited speaker at the Northeast Regional Meeting of the Association of Reproductive Managers to discuss FDA's proposed regulation of assisted reproductive technology clinics.
4/22/03	FDA Presentation on "Science-based Testing for Biologics" at the National Research Council, Roundtable on Biomedical Engineering Materials and Applications
4/21/03	FDA Presentation at the Defense Advance Research Projects Agency (DARPA) on "FDA Regulatory Framework for Cell and Gene Therapy, including Engineered Tissues"
4/1/03	Keystone Symposia
3/28-31/03	AATB 7 th Annual Spring Meeting, "Bacterial Culturing of Human Tissue Allografts: AATB Interaction with FDA and CDC" and "Infections Reported to be Associated with AATB-Accredited Entities: A Panel Discussion"
2/03	CBER Biologics Response Modifiers Advisory Committee Meeting on Hematopoietic Stem Cell Transplantation
12/02	Scheduled site visit at the Shady Grove Fertility Center
11/18/02	National Coalition for Oversight of Assisted Reproductive Technologies (NCOART) Meeting
11/9/02	University of Kentucky – Developing a Compliant Practice: The FDA comes to ART

11/4-5/02	Workshop on Development of Donor Screening Assays for West Nile Virus – ASRM participation
11/1/02	FDA discussion with CAP staff concerning comparison of standards with GTP proposed requirements
11/02	Workshop on Development of Donor Screening Assays for West Nile Virus (both blood and tissues discussed)
11/02	FDA Presentation at the AATB QA Workshop, New Orleans
11/02	Part 15 Hearing on Combination Products
11/02	FDA/ORA/CBER Tissue Training Course for FDA Inspectors
10/21-25/02	Human Tissue Establishment Inspection Training Course
10/16/02	ASRM Annual Meeting: FDA Update
9/21/02	FDA invited speaker to the 3 rd Annual Embryology Summit Conference at the Mayo Clinic, Rochester, Minn. To discuss FDA's proposed regulation of embryology laboratories.
9/18-19/02	FDA/NIH/DHHS Workshop on Evidence Based Assisted Reproductive Technologies
8/02	AATB/FDA Workshop on Bacterial Contamination
6/02	TSE Advisory Committee – Validation of Procedures to Prevent Contamination and Cross-Contamination with TSE Agents; presentation of draft guidance on CJD/vCJD
6/02	FDA invited speaker at the 4 th International Donor Registry Conference in Oslo, Norway, to discuss FDA's proposed regulatory framework for Hematopoietic stem cells.
5/9/02	CBER Biological Response Modifiers Advisory Committee meeting on Ooplasm transfer
3/24-26/02	AATB 6 th Annual Spring Meeting – FDA Presentation on “Microbial Contamination and Cross Contamination Concerns During Processing of Tissue, an FDA Perspective”
1/02	TSE Advisory Committee—CJD/vCJD risk in tissue donors

12/01	CBER Biological Response Modifiers Advisory Committee on Risk Factors for Infectious Disease Transmission by Artificial Insemination
11/28/01	FDA Presentation at the AATB QA Workshop, Tempe, AZ
10/01	Workshop at RAPS Annual Meeting – Human Reproductive Cells and Tissues
8/29/01	FDA's Tissue Reference Group Workshop
6/01	FDA Presentation at the EBAA Annual Meeting, Tucson, AZ
5/3/01	FDA/EBAA Meeting regarding GTP Issues
4/16/01	FDA/ASRM Meeting – GTP Proposed Regulation
10/3/00	RAPS Meeting
8/14-15/00	Workshop: Unrelated Allogeneic Cord Blood Banking and Transplant Forum
8/2/00	Open Public Meeting - Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair
6/00	CDC Donor Suitability Workshop
2/10/00	FDA/ASRM Meeting Concerning the Donor Suitability Proposed Regulation
2000	Tissue Engineering course
11/17-19/99	AATB QA Workshop, New Orleans, LA - FDA Review of Tissue Bank Inspections; Status of Required Serology Testing, Update Regarding Proposed Regulations
9/99	ASRM - Presentation - FDA Update on Regulation of Reproductive Cells and Tissue.
6/99	EBAA - Presentation on Registration Proposed Rule and Donor Suitability Proposed Rule
6/99	Institute of Science, Law and Technology (ISLAT) informational meeting with FDA to discuss ART issues

4/8/99	Human Tissue Industry Seminar hosted by ASQ and Los Angeles District, Los Angeles, CA
4/99	RESOLVE consumer association informational meeting with FDA to discuss ART issues
3/99	AATB - Presentation on Donor Suitability Proposed Rule
12/98	FDA Science Forum on Proposed Approach
11/98	EBAA - Compliance with Final Rule
10/98	ASRM - FDA update on Regulation of Reproductive Cells and Tissue
9/10/98	Workshop: Hematopoietic Stem/Progenitor Cell Products: Discussion of Unrelated Allogeneic/Umbilical Cord Blood and Peripheral Blood Cell Banking and Transplantation
8/98	AATB Annual Meeting - FDA Update and Implications of FDA Regulation of Reproductive Tissue
7/98	AATB Informational meeting with FDA concerning establishment certification and standard development
6/98	EBAA Annual Meeting- Establishment Registration and Listing - proposed rule
5/98	AATB mid -year meeting - FDA - What's Ahead/CJD and Dura Mater
4/20/98	FDA/AATB Meeting Concerning Summary of Records
4/9/98	Videoconference arranged by FDA Southwest Region and Dallas District on the Regulation of Human Tissue Intended for Transplantation presented to EBAA members located in the Southwestern U.S.
3/98	Training and Review - Regulatory Issues in Tissue Banking
2/98	FDA presentation at CDC and RESOLVE (a federation of infertility patient associations) sponsored meeting "Approaches to A.R.T. Oversight: What's Best in the U.S."
12/23/97	Workshop: Ethical Issues in Cord Blood Banking

11/97	Meeting with Society of In-Vitro Biology - Proposed Approach
7/11/97	FDA/AATB - Discussion of Regulation of Demineralized Bone Matrix
6/23/97	Discussion of Regulation of Eye Tissue with EBAA
4/8/97	FDA meeting on Regulation of Eye Tissue with Eye Bank Representatives.
3/17/97	FDA Open Public Meeting for comments on the "Proposed Approach"
12/19/96	CBER/FACT meeting
12/96	FDA invited to discuss good tissue practices with AATB, EBAA and ASRM
12/12/96	FDA meeting with representatives on Cord and Peripheral Blood
12/11/96	FDA meeting with representatives of autologous and other cell therapies.
10/96	Heart valve industry - Discussion of regulation of heart valve allografts
12/13/95	Workshop: Cord Blood Stem Cells - Procedures for Collection and Storage
2/4/96	FDA meeting with representatives on conventional banked human tissue for transplantation, eye and reproductive tissue
10/95 and 3/96	FDA invited to discuss reproductive tissue donor testing, screening and establishment registration with ASRM and AATB
6/20-21/95	Tissue Workshop: Tissue for Transplantation and Reproductive Tissue: Scientific and Regulatory Issues and Perspectives
3/95	Workshop on Human Tissue Intended for Transplantation and Human Reproductive Tissue: Donor Screening and Infectious Disease Testing
6/94	Workshop on Human Tissue Intended for Transplantation

Planned Future Meetings with Industry:

10/03	Workshop at the ASRM Annual Meeting: FDA Regulations: What IVF Labs Need to Know
9/29/03	Center For Business Intelligence
5/28/03	International Society for Cellular Therapies –GTP Workshop (participation on organizing committee and presentations at the meeting)
5/15/03	Pittsburgh Development Center
5/12/03	Covance Laboratories, Inc.

FDA Investigator Training:

10/21-25/02	FDA Human Tissue Course for Investigators, Annapolis, MD
6/3-6/02	FDA Human Tissue Course for Investigators, Columbia, MD
2/9-11/99	FDA Central Region Human Tissue Course for FDA Investigators
3/12/97	Training Provided to Baltimore District Biologics Cadre regarding Inspection of Human Tissue Establishment
2/1-3/95	FDA Mid-Atlantic Region Tissue Bank Training for FDA Investigators, Baltimore, MD

Future Plans:

- “Human Tissue Inspection” course scheduled for 10/03
- FDA scientific workshops to gather information and data on ART practices
- FDA open public meeting to address questions concerning proposed rules on donor suitability and GTPS’s (after publication)
- Continue dialogue with ASRM/SART and AATB
- AATB and ASRM have agreed to hold site visit program at semen banks and infertility clinics for investigators in the District Offices as an educational and cross-training opportunity for FDA investigators in advance of FDA finalizing in 2004 the new 21 CFR Part 1271 regulations that would include reproductive tissues and cell establishment.
- Continue Dialogue with EBAA, AABB, FACT and ISHAGE

Leveraging Initiatives with the Cell/Tissue Industry:

- Continue Dialogue with EBAA and ASRM regarding developing a draft guidance document to implement the donor eligibility (DE) and GTP rules specifically for their industry

GLOSSARY

AABB	American Association of Blood Banks
AATB	American Association of Tissue Banks
ACOT	Advisory Committee on Organ Transplantation
ARM	Association of Reproductive Managers
ART	Assisted Reproductive Technologies
ASRM	American Society for Reproductive Medicine
ASQ	American Society for Quality
CAP	College of American Pathologists
CDC	Centers for Disease and Control
CJD	Creutzfeldt-Jakob Disease
DARPA.....	Defense Advance Research Projects Agency
DE	Donor Eligibility
DHHS	Department of Health and Human Services
EBAA	Eye Bank Association of America
FACT.....	Federation for Accreditation of Cellular Therapies
FDA	Food and Drug Administration
FDLI	Food and Drug Law Institute
GTP	Good Tissue Practices
HRSA	Health Resources and Services Administration
ISHAGE.....	International Society for Hematopoietic and Graft Engineering
ISLAT	Institute of Science, Law and Technology
NCOART.....	National Coalition for Oversight of Assisted Reproductive Technologies
NIH	National Institutes of Health
RAPS	Regulatory Affairs Professional Society
RESOLVE.....	National Infertility Association
SART	Society for Assisted Reproductive Technologies
vCJD	variant Creutzfeldt-Jakob Disease

PAGE 1 SHEET 1 LYNKIN VS. CRYOLIFE, ET AL.

IN THE SUPERIOR COURT OF COBB COUNTY
STATE OF GEORGIA

STEVE LYKINS,
PLAINTIFF,
V.
CRYOLIFE, INC.,
DEFENDANTS.

CIVIL ACTION
NUMBER
02105613-24

THE DEPOSITION OF JAMES C. VANDER WYK, PH.D.,
TAKEN ON TUESDAY, JANUARY 21, 2003 ON BEHALF OF THE
PLAINTIFF, AT APPROXIMATELY 9:00 A.M., AT HAWKINS &
PARNELL, 4000 SUNTRUST PLAZA, 303 PEACHTREE STREET,
SUITE 40, ATLANTA, GEORGIA, BEFORE KIMBERLY S. GREENE,
CERTIFIED COURT REPORTER, B-1708.

ATLANTA WEST REPORTERS
CERTIFIED COURT REPORTER
P.O. BOX 107
CLARKSBURG, MARYLAND 20811
(703)732-8897

PAGE 3

I N D E X
CROSS-EXAMINATION BY MR. ALLEN: PAGE 4.

E X H I B I T S

NUMBER	DESCRIPTION	PAGE
P-01	11/14/97 LETTER TO MR. ANDERSON	29
P-02	CDC ARTICLE - MMWR 3/26/98	33
P-03	12/1/97 LETTER TO DR. DOCTOPHER	55
P-04	12/1/97 MEMO FROM DR. VANDER WYK	67
P-05	PRINTOUT FROM MAUDS DATABASE - 6/28/01	73
P-06	PRINTOUT FROM MAUDS DATABASE - 6/28/01	73
P-07	PRINTOUT FROM MAUDS DATABASE - 4/11/01	73
P-08	11/12/01 11:18 PM E-MAIL FROM M. KADNER	93
P-09	11/12/01 11:18 PM E-MAIL FROM M. KADNER	94
P-10	12/17/01 2:26 PM E-MAIL FROM M. KADNER	97
P-11	12/17/01 2:26 PM E-MAIL FROM M. KADNER	98
P-12	12/14/01 PRESS RELEASE FROM M. KADNER	107
P-13	C-02693 PRESS RELEASE - 12/14/01	118
P-14	PRINTOUT FROM MAUDS DATABASE - 1/15/99	120
P-15	1/3/02 LETTER TO DR. VANDER WYK	123
P-16	PRESS RELEASE - 1/23/02	148
P-17	1/23/02 LETTER FROM M. KADNER	149
P-18	5/12/02 LETTER FROM M. KADNER	149
P-19	CDC ARTICLE - MMWR 3/16/02	155
P-20	3/16/02 LETTER TO DR. VANDER WYK	161
P-21	3/2/01 LETTER TO DR. VANDER WYK	161
P-22	4/1/02 LETTER TO DR. VANDER WYK C-02693	166
P-23	4/7/02 LETTER TO DR. VANDER WYK C-02693	166
P-24	4/4/02 LETTER TO DR. VANDER WYK C-02693	191
P-25	C-02386 PRESS RELEASE - 4/23/02	194
P-26	5/17/02 LETTER TO DR. VANDER WYK	195
P-27	5/17/02 LETTER FROM M. KADNER	198
P-28	5/15/02 LETTER TO RALPH H. GRAHAM	202
P-29	5/17/02 LETTER TO STEVEN G. ANDERSON	203
P-30	5/17/02 LETTER TO STEVEN G. ANDERSON	203
P-31	6/13/02 RECAL ORDER	209
P-32	6/13/02 RECAL ORDER	209
P-33	PRESS RELEASE - 7/5/02	212
P-34	PRESS RELEASE - 6/14/02	214
P-35	REJECTED MEMO - 6/29/97, FROM A. REACOX	215

KIMBERLY S. GREENE, CCR.

Committee on Governmental Affairs

EXHIBIT #1

PAGE 2

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PAGE 4

P R O C E E D I N G S

1 MR. ALLEN: ANY STIPULATIONS YOU WANT TO
2 PUT ON? EVERYBODY JUST -- WE'RE GOING TO WAIVE
3 FORMALITIES, RESERVE OBJECTIONS EXCEPT TO THE
4 FORM OF THE QUESTION AND RESPONSIVENESS OF THE
5 ANSWER TELL THE TIME OF USE OF THE DEPOSITION.

6 MR. MAJOR: THAT'S --

7 MR. ALLEN: I'M ASSUMING HE'S GOING TO
8 READ AND SIGN.

9 MR. MAJOR: HE WILL READ AND SIGN, AND
10 LET'S HAVE THE SAME STIPULATION WE'VE HAD IN THE
11 OTHER DEPOSITIONS, THAT WE'LL HAVE 20 DAYS FROM
12 THE RECEIPT OF THE TRANSCRIPTS TO FILE OUR
13 CONFIDENTIAL DESIGNATIONS.

14 MR. ALLEN: YOU GOT IT.

15 WHEREUPON,

16 JAMES C. VANDER WYK
17 WAS CALLED AS A WITNESS AND, HAVING FIRST BEEN DULY
18 SWORN, WAS EXAMINED AND TESTIFIED AS FOLLOWS:

CROSS-EXAMINATION

BY MR. ALLEN:

21 Q GOOD MORNING, SIR. COULD YOU STATE YOUR
22 NAME AND PRESENT RESIDENTIAL ADDRESS FOR THE RECORD FOR
23 ME?

24 A YES. JAMES C. VANDER WYK, 638 GOLDENWOOD

SC 002417

25 Q OKAY. THEN WHY WAS THAT CUTOFF TIME PUT
1 IN PLACE?
2 A AT THE TIME THAT THAT WAS PUT IN PLACE,
3 CRYOLIFE WAS DOING A GREAT DEAL OF RESEARCH ASSOCIATED
4 WITH BEING ABLE TO SUPPLY SUITABLE TISSUE. SUITABLE
5 TISSUE HAS A LOT OF PARAMETERS TO IT, AND ONE OF THEM IS
6 THE VIABILITY AND PERFORMANCE CHARACTERISTICS OF THE --
7 OF THE TISSUE. AND SO WE HAD BEEN LOOKING AT A -- A
8 POINT WHERE THE TWO -- WHERE THE TISSUE WOULD STILL BE
9 SUITABLE, THAT THE PERFORMANCE CHARACTERISTICS WERE
10 CORRECT AND WE LOOKED TO IT UP TO THAT. WE JUST DIDN'T
11 LOOK ANYTHING PAST THAT, BUT IT WAS NOT IN THE CONTEXT
12 OF -- OF INFECTION RISK OR ANYTHING LIKE THAT.
13 Q WOULD A TISSUE THAT TESTED POSITIVE FOR
14 CLOSTRIDIUM BE SUITABLE Viable TISSUE?
15 A IF WE HAD A TISSUE, AN ALLOGRAFT, THAT
16 TESTED FOR CLOSTRIDIUM, IT WOULD HAVE BEEN DISCARDED.
17 Q SO THAT WOULD NOT BEEN A Viable TISSUE.
18 UNDER YOUR DEPOSITION -- OR YOUR DEFINITION. IS THAT
19 CORRECT?
20 A I WOULD RATHER NOT USE THE WORD "Viable"
21 CAUSE Viable MEANS SOMETHING DIFFERENT TO ME AS TISSUE
22 HAS LIVING CELLS IN IT. SUITABLE, IF -- IF TISSUE WERE
23 DETERMINED TO HAVE HAD ANY NUMBER OF MICROORGANISMS ON
24 IT BY TESTING, WE WOULD HAVE DISCARDED THAT OR DONE
25

26 ADDITIONAL TESTING TO ASSURE OURSELVES THAT WE KNEW IT
1 DID NOT HAVE SOMETHING ON IT.
2 Q SO IN 2002 -- OR EXCUSE ME, 2001 DID
3 CRYOLIFE, TO YOUR KNOWLEDGE, EVER TEST ANY TISSUE THAT
4 HAD CLOSTRIDIUM IN IT BEFORE PROCESSING IT?
5 A YES.
6 Q AND DID THAT TISSUE END UP GOING OUT TO --
7 TO A RECIPIENT, TO YOUR --
8 A I CANNOT TELL YOU THAT.
9 Q WHEN THAT TISSUE WAS -- WAS TESTED FOR
10 CLOSTRIDIUM, DID YOU THEN GO AHEAD AND PROCESS THE
11 TISSUE AND THEN TEST IT AFTER PROCESSING?
12 A CORRECT.
13 Q AND AFTER IT WAS TESTED AFTER PROCESSING,
14 DID IT TEST POSITIVE STILL FOR CLOSTRIDIUM?
15 A IN ANY SPECIFIC CASE HAD IT, IT WOULD HAVE
16 BEEN REJECTED.
17 Q REJECTED. BUT IF IT TESTED POSITIVE
18 BEFORE CLOSTRIDIUM AND THEN YOU -- THEN YOU
19 PROCESSED IT AND THEN IT CAME OUT OKAY ACCORDING TO YOUR
20 TESTING, THEN YOU WOULD HAVE ALLOWED IT TO BE USED BY A
21 RECIPIENT. CORRECT?
22 A THAT IS MY UNDERSTANDING.
23 Q AND IF A TISSUE FROM A DONOR TESTED
24 POSITIVE FOR CLOSTRIDIUM IN 2001 AND IT WAS DISCARDED
25

27 AND THERE WERE OTHER TISSUES FROM THAT SAME DONOR THAT
1 DID NOT TEST POSITIVE FOR CLOSTRIDIUM. YOU WOULD HAVE
2 ALLOWED THOSE TISSUES OUT TO THE -- TO THE RECIPIENT.
3 CORRECT?
4 A THE TISSUE ASSOCIATED WITH THE POSITIVE
5 CLOSTRIDIUM TEST WOULD HAVE BEEN DISCARDED. TISSUES IN
6 SEPARATE TESTS -- REPRESENTED BY SEPARATE TESTS THAT DID
7 NOT TEST POSITIVE FOR THAT WOULD HAVE BEEN FOUND
8 SUITABLE BASED ON THAT CHARACTERISTIC.
9 Q ARE YOU AWARE OF ANYBODY ELSE IN THE
10 INDUSTRY THAT WOULD HAVE DONE THAT?
11 A YES.
12 Q WHO?
13 A IT IS MY UNDERSTANDING THAT EVERYONE WOULD
14 HAVE.
15 Q SO YOU UNDERSTAND THAT EVERYBODY IN YOUR
16 INDUSTRY, IF ONE TISSUE HAD TESTED POSITIVE FOR
17 CLOSTRIDIUM, THEY WOULD HAVE STILL SHIPPED OTHER TISSUES
18 FROM THAT SAME DONOR IF IT -- THEY WERE NEGATIVE FOR
19 CLOSTRIDIUM.
20 A IF THE TISSUE TESTING POSITIVE -- FIRST, I
21 CAN'T TELL YOU WHETHER THEY WOULD HAVE REJECTED IT.
22 WHAT I'M SAYING IS THAT OTHER TISSUE THAT HAD NOT TESTED
23 POSITIVE FOR THAT BACTERIUM OR ANY OTHER BACTERIUM. IT
24 IS MY UNDERSTANDING IF NOT ALL, NEARLY ALL WOULD HAVE

28 SHIPPED THAT TISSUE. AND I BELIEVE THAT'S STILL THE
1 CASE TODAY.
2 Q IN 2001 CRYOLIFE DIDN'T TEST THE TISSUE
3 COMING IN TO CRYOLIFE BEFORE IT WAS PUT IN THAT -- I
4 THINK YOU CALL IT THE ANTIBIOTIC/ANTIMICROBIAL COCKTAIL?
5 A CORRECT.
6 Q AND WE'LL JUST CALL IT THE COCKTAIL FROM
7 HERE. HOW'S THAT?
8 A OKAY.
9 Q SO YOU WOULD HAVE TESTED THE TISSUE AFTER
10 IT SOAKED IN THE COCKTAIL.
11 MR. MAJOR: WELL, LET ME OBJECT. I THINK
12 THAT'S AN INCOMPLETE DESCRIPTION. TO THE EXTENT
13 YOU DESIRE TO CALL IT A COCKTAIL, I'D ASK YOU TO
14 CALL IT THE ANTINICROBIAL COCKTAIL.
15 MR. ALLEN: WE'LL DO THAT. IT'S EASY
16 ENOUGH.
17 BY MR. ALLEN:
18 Q SO IN 2001 CRYOLIFE WOULD HAVE -- FOR THE
19 FIRST TIME WOULD HAVE TESTED ANY TISSUE AFTER IT WAS IN
20 THE ANTINICROBIAL/ANTIBIOTIC COCKTAIL. CORRECT?
21 A AT ANY TIME IN OUR HISTORY WE WOULD HAVE
22 DONE THAT.
23 Q AND YOU'VE BEEN DOING THAT SINCE 1996, AT
24 LEAST TO YOUR KNOWLEDGE, RIGHT?

1 A AT LEAST SINCE 1996.
 2 Q ARE YOU AWARE OF HOW LONG CRYOLIFE HAD
 3 BEEN DOING THAT BEFORE 1996?
 4 A I CANNOT GIVE YOU AN EXACT ANSWER. MY
 5 UNDERSTANDING IS VIRTUALLY FOREVER.
 6 Q SINCE THE BEGINNING.
 7 A ESSENTIALLY.
 8 Q WHEN DID CRYOLIFE START?
 9 A MY UNDERSTANDING IS 1984.
 10 Q NOW WHAT LED YOU TO COME TO CRYOLIFE?
 11 A SPECIFICALLY TO COME TO CRYOLIFE. I HAD
 12 BEEN INVOLVED IN THE MEDICAL DEVICE INDUSTRY AND HAD A
 13 GREAT -- I CONSIDERED A GREAT DEAL OF EXPERIENCE IN
 14 THAT. CRYOLIFE WAS, AND THE WHOLE INDUSTRY WAS MOVING
 15 TO BECOMING MORE MEDICAL DEVICE-LIKE AS OPPOSED TO A
 16 VOLUNTARY TISSUE PROCUREMENT, SMALL SCALE INDUSTRY AND
 17 WANTED TO HAVE MORE OF MEDICAL DEVICE TYPE FRAMEWORK, SO
 18 I BROUGHT THAT BACKGROUND. THE WHOLE NEW CATEGORY OF
 19 TISSUE -- OR TISSUE WAS A WHOLE NEW CATEGORY TO ME SO
 20 THERE WAS A BASIC INTEREST TO -- TO LOOK AT A DIFFERENT
 21 INDUSTRY AND YET APPLY THE SKILLS THAT I THOUGHT I
 22 BROUGHT.
 23 Q DID THEY COME TO YOU OR DID YOU GO TO
 24 THEM?
 25 A I -- MY -- MY RECOLLECTION WAS THAT I SAW

25

1 AN ADVERTISEMENT. I WAS LOOKING FOR A DIFFERENT
 2 POSITION, APPLIED TO THE ADVERTISEMENT. THEY RESPONDED
 3 IN THE NORMAL COURSE OF EVENTS AND EVENTUALLY HIRED ME.
 4 Q DO YOU CONSIDER THE ORTHOPEDIC TISSUE
 5 PROCESS BY CRYOLIFE TO BE A MEDICAL DEVICE TYPE OF -- AS
 6 YOU --
 7 A NO. IT'S NOT A --
 8 MR. MAJOR: OBJECT TO THE FORM. CALLS FOR
 9 A LEGAL CONCLUSION.
 10 THE DEFENDANT: EXCUSE ME?
 11 MR. MAJOR: GO AHEAD, YOU CAN ANSWER THE
 12 QUESTION.
 13 THE DEFENDANT: OKAY. I'LL BE TECHNICAL IN
 14 THE SENSE THAT ORTHOPEDIC TISSUE IS NOT
 15 CLASSIFIED FROM A REGULATORY SCHEME AS A MEDICAL
 16 DEVICE. I WAS TALKING MORE COLLOQUIAL TERMS
 17 ABOUT HERE IS SOMETHING THAT IS IMPLANTED IN
 18 SOMEONE.
 19 BY MR. ALLEN:
 20 Q SO IT'S MORE OF A MEDICAL DEVICE AS IT
 21 RELATES TO -- TO YOUR DEFINITION OF MEDICAL DEVICE
 22 'CAUSE IT'S IMPLANTED IN SOMEBODY. IS THAT...
 23 A IT'S -- AN ALLOGRAFT IS INTENDED, BY
 24 DEFINITION, TO MITIGATE THE DISEASE STATE, TO HELP
 25 SOMEBODY, IMPROVE THEIR LIFESTYLE, SAVE THEIR LIFE.

30

1 THOSE KINDS OF THINGS, SO IN THAT -- IN THAT SENSE AS A
 2 WORKING OPERATION, BUT REGULATORILY IT IS NOT AT ALL.
 3 Q WHAT PART OF CRYOLIFE WOULD YOU -- AS YOU
 4 UNDERSTAND THE REGULATIONS -- BEING MEDICAL DEVICE?
 5 A EXCUSE ME?
 6 Q WHAT PART OF CRYOLIFE'S PRODUCT WOULD BE
 7 CONSIDERED MEDICAL DEVICE AS IT GOES THROUGH REGULATION?
 8 A THE BIOGLUE SURGICAL ADHESIVE IS A CLASS
 9 III MEDICAL DEVICE. THEY NEEDED SOMEBODY TO DEAL WITH
 10 THE REGULATORY ISSUES THERE. THE HUMAN HEART ALLOGRAFT
 11 WAS CLASSIFIED AS A MEDICAL DEVICE, BUT FUNDAMENTALLY
 12 REGULATED AS A TISSUE.
 13 Q NOW IN -- IN 1997 YOU'RE AWARE THAT
 14 CRYOLIFE RECEIVED A LETTER BY CERTIFIED MAIL FROM THE
 15 ACTING DISTRICT DIRECTOR OF THE FLORIDA DISTRICT OF THE
 16 FDA?
 17 A I'M -- I'M SURE YOU'RE READING FROM
 18 SOMETHING THAT YOU'RE AWARE OF. I DON'T KNOW THE
 19 SPECIFIC THING THAT YOU ARE REFERRING TO.
 20 MR. ALLEN: WE'LL MARK EXHIBIT 1.
 21 (WHEREUPON, PLAINTIFF'S EXHIBIT NO. 1 WAS
 22 MARKED FOR IDENTIFICATION.)
 23 BY MR. ALLEN:
 24 Q AND THIS'LL BE EXHIBIT 1. LETTER'S DATED
 25 NOVEMBER 14, 1997. IT'S ADDRESSED TO MR. ANDERSON FROM

1 MICHAEL CHAPPELL, ACTING DISTRICT DIRECTOR OF THE
 2 FLORIDA DISTRICT OF THE FDA.
 3 A UH-HUH. WELL, IF YOU HAVE SPECIFIC
 4 THINGS, I'LL HAVE TO GO BACK TO IT. I WAS JUST
 5 GENERALLY FAMILIARIZING MYSELF WITH THIS. YES.
 6 Q OKAY. NOW I'LL ASK YOU SOME SPECIFICS, SO
 7 YOU WOULD HAVE BEEN AWARE OF THAT LETTER IN YOUR
 8 CAPACITY IN 1997.
 9 A YES. THIS LETTER TO A DIVISION OF
 10 CRYOLIFE RIGHT HERE, IDEAS FOR MEDICINE, WE HAD
 11 PURCHASED JUST -- JUST PRIOR TO THIS, ESSENTIALLY.
 12 Q SO YOU'RE -- I'M GOING TO GO FROM PAGE --
 13 START ON PAGE ONE, THIRD FULL PARAGRAPH. (READING) THE
 14 INSPECTION REVEALED THAT THE DEVICES ARE ADULTERATED
 15 WITHIN THE MEANING OF SECTION 401(h) OF THE ACT -- IT
 16 CITES THE ACT ABOVE -- IN THAT THE METHODS USED IN, OR
 17 THE FACILITIES OR CONTROLS USED FOR MANUFACTURE,
 18 PROCESSING, PACKAGING, STORAGE OR DISTRIBUTION ARE NOT
 19 IN CONFORMANCE WITH THE QUALITY SYSTEM REGULATIONS.
 20 DID I READ THAT RIGHT SO FAR?
 21 A CORRECT.
 22 Q (READING) THESE VIOLATIONS INCLUDE BUT ARE
 23 NOT LIMITED TO THE FOLLOWING: FIRST INJECTION FROM THE
 24 PARAGRAPH, FAILURE TO IMPLEMENT CORRECTIVE AND
 25 PREVENTATIVE (SIC) ACTION FOR THE RECURRENCE OF

PAGE 69 LYKINS VS. CRYOLIFE, ET AL.

1 Q RIGHT. SO I MEAN YOU AT CRYOLIFE AND THE
 2 POLICIES THAT YOU PUT FORTH, YOU REALIZE THAT WHAT
 3 YOU'RE TRYING TO DO IS MITIGATE THE RISK OF INFECTION AS
 4 WE TALKED ABOUT, AND -- CORRECT?

5 A CORRECT.

6 Q AND THAT YOU PUT FORTH POLICY AND
 7 PROCEDURES OF INFORMATION THAT YOU KNOW WILL MITIGATE
 8 THAT RISK OF INFECTION. CORRECT?

9 A CORRECT.

10 Q AND --

11 A WE DO A LOT OF -- EXCUSE ME.

12 Q OKAY.. AND -- AND --

13 MR. MAJOR: WELL, GO AHEAD AND FINISH YOUR
 14 ANSWER.

15 THE DEFENDANT: WE DO A LOT OF RESEARCH.
 16 FOR EXAMPLE, THE INDUSTRY STANDARD, AS DESCRIBED
 17 IN SEVERAL OF THESE ARTICLES, WAS TO DO THINGS
 18 LIKE USE AN ANTIMICROBIAL SOLUTION AND -- AND THE
 19 ARTICLE SEEKS TO INDICATE THAT THAT IS A VERY
 20 WORTHWHILE ENDEAVOR, AND THEN THEY DO IT AT A
 21 TEMPERATURE THAT OUR RESEARCH SHOWS IS
 22 INFECTIVE. WE DID ADDITIONAL RESEARCH TO SHOW
 23 THAT THERE WAS A BETTER WAY TO DO THAT AND SO WE
 24 DID NOT FOLLOW THE INDUSTRY ACCEPTED MORALITY
 25 BECAUSE WE FELT IT DIDN'T WORK AND HAD DATA TO

PAGE 71

1 OBVIOUSLY ANY VALVE OR ANY ALLOGRAFT THAT IS DISCARDED
 2 IS REDUCING THE SUPPLY. I MEAN ON AN ESOTERIC, YOU
 3 KNOW, PER SE BASIS, I'M TALKING ABOUT THERE ARE THINGS
 4 ONE COULD IMPLEMENT THAT SEVERELY IMPACT THE
 5 AVAILABILITY WITHOUT A COMMENSURATE INCREASE OR --
 6 EXCUSE ME, DECREASE IN RISK. YOU CAN DEFINE A SPECIFIC
 7 REDUCTION THAT MAY BE VERY SMALL COMPARED TO THE HUGE
 8 PROBLEM THAT WOULD EXIST IF PEOPLE WERE NOT ABLE TO GET
 9 THE ALLOGRAFTS IN THE FIRST PLACE. SO ON AN INDIVIDUAL
 10 BASIS, THERE IS -- THERE IS NO EFFORT ON THE PART OF
 11 CRYOLIFE TO FIND A WAY TO RELEASE THAT TISSUE. IF THE
 12 DATA IS THERE IN ANYTHING FROM PROCUREMENT
 13 ORGANIZATIONS PROVIDED TO US, WE DO LEAN ON THE SIDE
 14 OF -- OF SAFETY.

15 Q YOU LEAN ON THE SIDE OF SAFETY TO THE END
 16 RECIPIENT. CORRECT?

17 A YES.

18 Q IN EVERYTHING THAT YOU DO. CORRECT?

19 A THAT IS THE ATTEMPT. THAT'S WHAT --

20 THAT'S WHAT IS CONSIDERED FIRST.

21 Q AND YOU TRY TO DO THINGS THAT ARE
 22 PRACTICAL, THAT WON'T SEVERELY REDUCE THE SUPPLY OF
 23 TISSUE. RIGHT?

24 A CORRECT.

25 Q YOU TRY TO MAKE SURE THE TISSUE COMES OUT

DEFENDANT: DR. JAMES VANDER VEN

PAGE 70

69
 1 INDICATE THAT. SO WE HAVE DEVIATED FROM INDUSTRY
 2 STANDARDS WHERE OUR INDICATIONS ARE THERE'S A,
 3 BETTER WAY TO DO IT.

4 BY MR. ALLEN:

5 Q AND WHEN YOU FIND A BETTER WAY TO REDUCE
 6 THE RISK OF INFECTION, YOU WANT TO DO IT. RIGHT?

7 A WE OF COURSE NEED TO DISCUSS THAT. WE
 8 NEED TO FIND OUT WHETHER IT'S A PRACTICAL THING TO DO.
 9 YOU CAN GET VERY ESOTERIC IN THOUGHT PROCESSES. IT HAS
 10 TO -- IT HAS TO WIND UP HAVING AN ALLOGRAFT THAT COMES
 11 OUT, YOU KNOW, AT THE END OF THE -- OF THE PROCESS, AND
 12 IT HAS TO NOT DAMAGE THE SUPPLY TO THE -- IN THE POINT
 13 WHERE PEOPLE ARE ADVERSELY AFFECTED. A CHILD WHO NEEDS
 14 A HEART VALVE NEEDS A HEART VALVE, AND IF HE DOESN'T GET
 15 IT, IN MANY CASES THESE CHILDREN DIE, SO I'M FORCED:
 16 EVERY DAY TO DEAL WITH THE REALITIES OF THIS -- OF THIS
 17 BALANCE. HOWEVER, ANY TEST THAT I KNOW THAT I KNOW I'VE
 18 GOT SOMETHING WRONG WITH THAT ALLOGRAFT, IT IS
 19 DISCARDED.

20 Q AND SO WHEN YOU TALK ABOUT DOING THINGS
 21 THAT -- THAT CAN REDUCE THE RISK OF INFECTION OR
 22 MITIGATE THE RISK OF INFECTION THAT ARE PRACTICAL, WE'RE
 23 TALKING ABOUT PRACTICAL MEANING NOT REDUCING THE SUPPLY
 24 OF ALLOGRAFTS OUT INTO THE PUBLIC. RIGHT?

25 A NO, I DIDN'T -- I DIDN'T SAY THAT.

PAGE 72

71
 1 USEFUL IN THE END RESULT TO THE PATIENT. RIGHT?

2 A THAT WOULD BE THE INTENT, THAT THE TISSUE
 3 BE USEFUL TO THAT PATIENT. THERE ARE THINGS WE COULD DO
 4 THAT WOULD REDUCE THE -- OR ELIMINATE THE RISK OF
 5 INFECTION FROM THE TISSUE, BUT THE TISSUE WOULD BE NOT
 6 SUITABLE AT ALL FOR ITS INTENDED PURPOSE. IT WOULD BE,
 7 IN EFFECT, COLLOQUIALLY, RUINED.

8 Q NOT THE PRE-TESTING -- PRE-PROCESSING
 9 TESTING WE TALKED ABOUT, IS IT -- IN 1996 AND EARLY '97
 10 WAS IT -- WAS IT A WASTE OF TIME, IN YOUR OPINION?

11 A WHEN -- WHEN THAT PRE-PROCESSING TISSUE
 12 TESTING WAS REVIEWED IN THE CONTEXT OF THAT TIME, IT
 13 APPEARED AS THOUGH THERE WAS NO LONGER A COMMENSURATE
 14 BENEFIT FROM DOING IT. THERE HAD BEEN A LOT OF REASONS
 15 FOR INSTITUTING IT PRIOR TO THAT. I AM NOT FULLY AWARE
 16 OF WHAT THEY ARE AND I'M NOT VERY CONVERSANT ON THAT.
 17 BUT THERE WERE REASONS TO DO THAT -- BUT AS THINGS
 18 PROGRESSION, WE LEARNED MORE, GOT MORE DATA, APPROVED
 19 VARIOUS PROCESSES, THINGS LIKE THAT. IT DID NOT APPEAR
 20 THAT CONTINUING IT DECREASED THE RISK THAT WE COULD
 21 UNDERSTAND.

22 Q SO CONTINUOUS PRE-PROCESSING TESTING ON
 23 THESE TISSUES, BASED UPON THE INFORMATION THAT YOU
 24 LEARNED AROUND '96/'97, THEREFORE IN YOUR OPINION --
 25 SCRATCH THAT.

KIMBERLY S. GREENE, CCR.

SC 002434

LYKINS VS. CHRYSLER, ET AL.

UNPUBLISHED - NOT FOR QUOTATION - 100-
PAGE 74

PRE-PROCESSING TISSUE IN '96/'97, BASED
UPON THE NEW INFORMATION THAT YOU HAD AT THAT TIME, LED
YOU TO BELIEVE THAT IT WAS NOT AN EFFICIENT USE OF TIME
TO PRE--PRE-PROCESS TEST TISSUES. IS THAT CORRECT?

A THAT'S REASONABLE.

Q SO --

A ONE NEEDS --

Q -- WAS BETTER SERVED --

A -- TO FOCUS ON IMPORTANT THINGS -- EXCUSE
ME, I INTERRUPTED.

MR. MAJOR: GO AHEAD IF YOU NEED TO
EXPLAIN THINGS.

MR. ALLEN: EXCUSE ME, I THOUGHT YOU WERE
FINISHED, I DON'T MEAN TO STOP YOU.

THE DEPUTY: YOU HAVE A MICROBIOLOGY LAB
THAT NEEDS TO DO A NUMBER OF THINGS AND YOU DO
WANT TO DO THINGS THAT ARE GOING TO CONTRIBUTE TO
THE END RESULT BENEFICIALLY. AND IF SOMETHING
ISN'T, AND THERE ARE OTHER THINGS THAT YOU CAN DO
AND WANT TO IMPLEMENT, IT SEEMS REASONABLE THAT
YOU WOULD GO AND DO THAT. IF SOMETHING IS NO
LONGER OF EFFECTIVENESS OR DOESN'T CONTRIBUTE TO
WHY -- TO THE SAME THINGS THAT YOU HAD INSTITUTED
IN THE FIRST PLACE, IT SEEMS REASONABLE THAT YOU
WOULD DISCONTINUE THAT.

BY MR. ALLEN:

Q SO YOU FELT IT WAS REASONABLE TO DISCONTINUE PRE- PRE-PROCESSING TESTING 'CAUSE YOU DIDN'T FEEL THAT IT HAD ANY OUTCOME ON THE END RESULT OF A -- OF A LOWERED RISK OF INFECTION TO THE PATIENT.

A WE DID NOT BELIEVE THAT THERE WAS ANY INCREASED RISK BY DISCONTINUING.

Q SO WHAT I SAID WAS TRUE.

A CORRECT, I JUST --

Q THAT'S FINE.

A -- RESTATED IT. SORRY.

Q AS WELL DID YOU FEEL IN 1995/97 THAT CONTINUING PRE-PROCESSING TESTING, THAT THAT'D BE A WASTE OF MONEY?

A WELL, OBVIOUSLY IF YOU'RE NOT DOING SOMETHING, THERE IS A REDUCTION IN EXPENDITURE AND MONIES THAT WE COULD WELL USE ON THINGS THAT WE HAVE DEMONSTRATED WERE VERY EFFECTIVE. BUT THAT'S NOT THE IMPLEMENTATION POINT OR THAT'S NOT THE CONSIDERATION. IT'S A CONSEQUENCE OF DOING IT, CERTAINLY. BUT IT WASN'T REALLY VERY SIGNIFICANT IN THE CONTEXT OF THE TOTAL BUDGET AND THE TOTAL PROCESSING COSTS. WE WERE ALWAYS IMPLEMENTING NEW TESTING.

(WHEREUPON, PLAINTIFF'S EXHIBIT NO. 4 WAS MARKED FOR IDENTIFICATION.)

PAGE 75

1 BY MR. ALLEN:

2 Q I'M GOING TO HAND TO YOU WHAT IS NOW
3 MARKED AS EXHIBIT 4. IT'S MARCH 3RD, '97 MEMO TO THE
4 TECHNICAL STEERING COMMITTEE FROM YOU, BATES STAMPED C-
5 05237 THROUGH 05239.

6 A (REVIEWS! UH-HUH.)

7 Q YOU KNOW THAT DOCUMENT?

8 A YES.

9 Q I READ YOU THE FIRST SENTENCE. IT IS
10 PROPOSED TO IMMEDIATELY DISCONTINUE THE PRACTICE OF
11 ROUTINE PRETREATMENT MICROBIOLOGICAL BIOPSY TESTING
12 OF HEART, VEIN AND ARTERY DONATIONS. BASED UPON '96
13 VOLUMES EXTRAPOLATED TO 1997, SAVINGS OF APPROXIMATELY
14 \$90,000 IN ONGOING SUPPLIES, TIME AND OUTSIDE LAB
15 TESTING CAN BE REALISTICALLY ACHIEVED. DID I READ THAT
16 CORRECT?

17 A YES.

18 Q SO PART OF YOUR THOUGHT PROCESS OF ENDING
19 THE PRETREATMENT TESTING WAS TO SAVE WHAT WAS PROJECTED
20 AT THAT TIME TO BE \$90,000. TRUE?

21 A NO, THAT WASN'T THE REASON THAT IT WAS
22 PROPOSED. I WOULD -- I CONSTANTLY REVIEW
23 MICROBIOLOGICAL LAB PROCEDURES. WE WERE USING THE PRE-
24 PROCESSING CULTURES AS AN ADJUNCT TO THE FINISHED
25 ALLOGRAFT TESTING TO BE ABLE TO ANALYZE THE POSSIBILITY

1 OF AN ENVIRONMENTAL CONTAMINANT VERSUS A TISSUE
2 CONTAMINANT, SO THE TESTING WAS BEING USED. WHEN I
3 LOOKED THROUGH THE SITUATION, ANOTHER SENTENCE THERE
4 SAYS ELIMINATING THE TESTS WOULD HAVE CAUSED AN ISSUE,
5 BUT BY PUTTING ANOTHER TEST BACK IN AT THE END, WE WOULD
6 GET EQUIVALENT ASSURANCE THAT THE END RESULT BEING
7 CORRECT, OKAY? SO WE DISCONTINUED ONE, WE ADDED
8 ANOTHER. THERE WAS AN ISSUE WHERE SOME MONEY WOULD BE
9 SAVED BY NOT DOING THE TEST. MY FIDUCIARY
10 RESPONSIBILITY AS A LAB, YOU KNOW, EXECUTIVE, MANAGER,
1 TO EFFICIENTLY USE THE RESOURCES THAT ARE GIVEN TO ME, I
2 APPLIED SOME OF THOSE RESOURCES TO ANOTHER TEST, BUT IT
3 WASN'T THE INITIAL ASPECT OF IT. LAB EFFICIENCY AND
4 DOING THINGS PRODUCTIVELY SO THAT THEY WOULD NOT BE
5 BURDEN -- DOING SOMETHING WHEN YOU COULD BE MORE
6 PRODUCTIVELY DOING ANOTHER TEST THAT WOULD HAVE MORE
7 GERMANE RESULTS WAS THE INTENT. IT DOES RESULT IN A
8 SAVINGS. YOU CAN'T DISCONTINUE SOMETHING WITHOUT HAVING
9 SOME SAVINGS TO IT. BUT AS AGAIN, THE \$90,000 WAS A --
10 IS NOT A LARGE NUMBER, AS I UNDERSTOOD IT. IN THE SCHEME
1 OF WHAT ALL OUR PROCESSING COSTS WERE.
2 Q BUT PART OF YOUR CONSIDERATION FOR
3 STOPPING THE PRE-PROCESSING TESTING WAS TO BE EFFICIENT
4 AND SAVE \$90,000.
5 A TO BE EFFICIENT IN THE LABORATORY AND IF

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SC 002435

LYKINS VS. CRYOLIFE, ET AL.

DEPONENT: DR. JAMES VANDER WYK

PAGE 77

77

1 RESULTED IN A \$90,000 SAVING, WITHOUT ANY INCREASED
 2 RISK.
 3 Q AND SINCE 1997 HAVE YOU REINITIATED PRE-
 4 PROCESSING TESTING?
 5 A YES, WE DID.
 6 Q WHEN DID YOU DO THAT?
 7 A I THINK WE DID IT IN PHASES, BUT MY BEST
 8 RECOLLECTION IS THAT WE REINSTITUTED SOME PRE-PROCESSING
 9 CULTURING IN JUNE OF 2002.
 10 Q AND WHY DID YOU DO THAT?
 11 A CUSTOMERS REQUESTED WE DO THAT.
 12 Q WHO?
 13 A I CAN'T GIVE YOU SPECIFIC CUSTOMERS.
 14 MARKETING SAID TO ME THAT YOU NEED TO DO THAT SO WE CAN
 15 RESPOND TO THE REQUESTS OF CUSTOMERS.
 16 Q DID YOU MAKE ANY ATTEMPT TO EXPLAIN TO THE
 17 CUSTOMERS IT WAS NOT NEEDED?
 18 A YES.
 19 Q WHAT WAS THE RESPONSE?
 20 A THEY WERE CONCERNED THAT THEY WANTED TO
 21 AVOID ANY APPEARANCE -- THEY DID NOT UNDERSTAND THE
 22 ISSUES, IN MY OPINION, IN MANY CASES. IN OTHER CASES
 23 THEY SAID YES, WE KNOW THAT, BUT WE WOULD JUST LIKE YOU
 24 TO DO THAT. IN ADDITION I BELIEVE IN SEVERAL INSTANCES
 25 THE LEGAL SYSTEM WITHIN THE HOSPITAL SIMPLY SAID THAT'S

PAGE 78

78

1 WHAT WE WANT TO DO AND HAVE, REGARDLESS OF THE SCIENCE
 2 OF IT. IT IS BENEFICIAL TO THE HOSPITAL FROM JUST --
 3 JUST THE SENSE OF DOING IT, SO WE REINSTITUTED IT FOR
 4 THAI REASON, BECAUSE WE HAD NO CHANGE OF THOUGHT PROCESS
 5 THAT IT MAKES A DIFFERENCE.
 6 Q SO THE PRE PROCESSING TESTING THAT WAS
 7 DONE IN JUNE OF 2002 WAS DONE BECAUSE IT -- OF MARKETING
 8 PURPOSES.
 9 MR. MAJOR: OBJECT TO THE FORM OF THE
 10 QUESTION. IT MISCHARACTERIZES HIS TESTIMONY.
 11 THE DEPONENT: WE HAD PEOPLE TO WHOM WE'RE
 12 SUPPLYING ALLOGRAFTS AND WE HAD PEOPLE WHO WERE
 13 SUPPLYING TISSUE THAT WOULD GENERATE ALLOGRAFTS
 14 WHO REQUESTED THAT WE IMPLEMENT THAT, FOR
 15 WHATEVER REASONS, AND THERE WERE A VARIETY OF
 16 REASONS -- AS I UNDERSTAND IT, 'CAUSE I RAD NO
 17 DIRECT CONTACT. I'M GIVING YOU MY UNDERSTANDING
 18 OF THE SITUATION, BUT IT CERTAINLY WASN'T DONE
 19 BECAUSE WE HAD DISCOVERED SOME DATA OR SCIENCE
 20 THAT SAID THAT WE HAD BEEN WRONG BEFORE.
 21 BY MR. ALLEN:
 22 Q SO THE BOTTOM LINE, YOU DIDN'T RESTART THE
 23 PRE-PROCESSING TESTING BECAUSE OF SOME SCIENTIFIC DATA
 24 THAT WAS PUT FORWARD TO YOU.
 25 A CORRECT.

PAGE 79

PAGE 80

1 Q AND SO THEN THE BASIC REASON THAT YOU
 2 STARTED PRE-PROCESSING TESTING WAS -- WAS TO ENSURE THE
 3 END CUSTOMER -- OR SCRATCH THAT.
 4 YOU RESTARTED PRE-PROCESSING TESTING
 5 BECAUSE YOUR CUSTOMER -- THE END CUSTOMER, THE HOSPITALS
 6 AND THE DOCTORS OUT THERE -- WANTED TO SEE IT DONE.
 7 A THERE WERE REQUESTS FROM PEOPLE SUPPLYING
 8 ALLOGRAFTS AND THERE WERE REQUESTS FROM PEOPLE WHO WERE
 9 USING ALLOGRAFTS, IT IS MY UNDERSTANDING, REQUESTED THAT
 10 WE DO THAT AND WE MUST MEET CUSTOMER NEEDS AND
 11 EXPECTATIONS.
 12 Q AND THAT'S THE ONLY REASON WHY YOU STARTED
 13 PRE-PROCESSING TESTING.
 14 A THAT IS THE ONLY REASON WE RESTARTED THAT
 15 PRE-PROCESSING CULTURE.
 16 Q AND BEFORE I LEAVE THAT HERO, THE --
 17 EXHIBIT 4, YOU -- YOU FEEL IN 1997 THAT THE SAVINGS OF
 18 \$90,000 WAS A MINOR CONSIDERATION IN STOPPING PRE-
 19 TESTING -- PROCESSING TESTING?
 20 A IT WAS CERTAINLY NOT THE DRIVING FORCE OR
 21 ANY PRIME -- PRIME REASON IT WAS IMPLEMENTED. THE VAST
 22 AMOUNT OF THE MENO GOES INTO HOW, IF WE PUT IN AN ADDED
 23 TEST AT THE END, WE WOULD MAKE UP FOR AND PROVIDE
 24 COMPLETE EQUIVALENT ASSURANCE ON THE ELIMINATION. IT
 25 JUST WASN'T ELIMINATED. THERE WAS ACCOMMODATION FOR

1 WHAT WE WERE USING THE TESTING FOR AND HOW TO
 2 ACCOMMODATE THAT MORE EFFICIENTLY.
 3 Q I JUST WANT TO FINISH READING THE REST OF
 4 THAT -- THAT FIRST PARAGRAPH. ADDITIONAL CONSIDERATIONS
 5 INCLUDE AVOIDING THE NEED TO ADD INCUBATOR AND LAB FLOOR
 6 SPACE, AS WELL AS A SECOND TIE -- WHICH IS, STANDS FOR?
 7 A FULL TIME EQUIVALENT.
 8 Q WHICH IS PERSONNEL?
 9 A PERSONNEL.
 10 Q OKAY. -- FOR THE EXPANDING PRE-TREATMENT
 11 WORKLOAD NOT PROVIDED FOR IN CURRENT LAB DESIGN, PERIOD,
 12 TO PROVIDE EQUIVALENT ASSURANCE TO THE CURRENT METHOD,
 13 APPROXIMATELY 1.5 PERCENT OF THE POST-TREATMENT CULTURES
 14 WOULD REQUIRE A RETEST WHICH IS NOT CURRENTLY PERFORMED
 15 DUE TO MATCH BETWEEN PRE- AND POST-TREATMENT ORGANISMS.
 16 DID I READ THAT RIGHT?
 17 A CORRECT.
 18 Q SO IN YOUR ESTIMATION, 1.5 PERCENT OF --
 19 OF TISSUES THAT CAME OUT OF PROCESSING WOULD -- WOULD
 20 NEED AN ADDITIONAL TEST. IS THAT CORRECT?
 21 A IN -- IN OUR REVIEW OF IT AND THE
 22 CIRCUMSTANCES OF HOW WE WERE USING THE RESULTS, WE
 23 DETERMINED THAT WE WOULD NEED TO ADD TESTING, WHICH WE
 24 DID, TO GIVE EQUIVALENT RESULTS.
 25 Q ON 1.5 PERCENT OF THE PRODUCT.

KINDERLY S. GREENE, CCR.

SC 002436

LYKINS VS. CRYOLIFE, ET AL.

PAGE 189

DEONENT: DR. JAMES VANDER WYK

PAGE 190

1 MARCH INSPECTION.
 2 THE DEONENT: CORRECT.
 3 BY MR. ALLEN:
 4 Q AND THE FORM 483 (SIC) MAKES NUMEROUS
 5 OBSERVATIONS. I THINK THERE'S A TOTAL OF 12
 6 OBSERVATIONS. AND YOU -- YOU'VE SEEN THIS DOCUMENT
 7 BEFORE. RIGHT?
 8 A YES, SIR.
 9 Q WHAT DO YOU UNDERSTAND A FORM 483 -- THE
 10 PURPOSE OF THE FORM 483?
 11 A THE PURPOSE OF FORM 483, AS I UNDERSTAND
 12 IT, IS TO INFORM A FACILITY THAT HAS BEEN INSPECTED THAT
 13 OBSERVATIONS, AS THEY'RE WRITTEN UP, WHICH PURPORT TO BE
 14 DIFFERENCES BETWEEN PRACTICES OBSERVED OR DATA OBSERVED
 15 AND WHAT THE FDA PURPORTS TO BE THEIR REGULATIONS
 16 ASSOCIATED WITH THAT. THIS INSPECTION AND THIS 483 I
 17 BELIEVE IS BASED UPON ELEMENTS OF A GUIDANCE DOCUMENT
 18 ISSUED TWO WEEKS PRIOR TO THE INSPECTION.
 19 Q AND THE GUIDANCE DOCUMENT, WHAT IS THAT?
 20 A THERE WAS A GUIDANCE DOCUMENT ISSUED, IF
 21 UNLESS I STAND CORRECTED, MARCH OF 2002 WHICH MADE
 22 A NUMBER OF STATEMENTS ABOUT WHAT THE FDA BELIEVED
 23 SHOULD BE PRACTICES OF A -- OF A COMPANY. THEY WERE NOT
 24 FORMAL REGULATIONS. THEY WERE OPINIONS, AND THEY WERE
 25 NOT IN EFFECT AT THE TIME THAT THE TISSUE -- OR THEY

189

1 WERE NOT IN EFFECT PRIOR TO MARCH 8TH, SO ALL OF THESE
 2 OBSERVATIONS ARE DERIVATIVE OF -- OF THAT DOCUMENT ON
 3 MARCH 8TH.
 4 Q SO THEY GAVE YOU A GUIDANCE DOCUMENT THE
 5 FIRST OF MARCH THAT SAID WE THINK YOU OUGHT TO BE DOING
 6 NUMEROUS THINGS. IS THAT RIGHT?
 7 A THEY -- THEY ISSUED --
 8 MR. MAJOR: HOLD ON JUST A -- LET ME
 9 OBJECT TO THE EXTENT THAT THE QUESTION IMPLIES
 10 THAT IT WAS GIVEN TO CRYOLIFE --
 11 THE DEONENT: I WAS GOING TO --
 12 MR. MAJOR: -- AND CRYOLIFE ONLY.
 13 THE DEONENT: -- MAKE THAT STATEMENT.
 14 BY MR. ALLEN:
 15 Q WELL, CORRECT ME WITH THAT THEN.
 16 A IT WAS ISSUED AS A GENERAL GUIDANCE
 17 DOCUMENT, NOT A REGULATION WITH THE FORCE OF LAW, AS A
 18 GENERAL OPINION ABOUT HOW THE FDA WOULD LIKE TO SEE
 19 ITEMS OCCUR. IT WAS ISSUED AS A GENERAL INDUSTRY ONE.
 20 IT WAS NOT DIRECTED, DID NOT STATE -- AND APPLIED
 21 APPARENTLY TO EVERYBODY.
 22 Q IT WAS A GUIDANCE DOCUMENT. WAS IT
 23 SPECIFIC TO CRYOLIFE?
 24 A NO.
 25 Q IT WAS A GUIDANCE DOC -- IT WAS SPECIFIC

190

PAGE 191

1 TO TISSUES PROCESSORS SUCH AS YOU.
 2 A IT WAS TO THE TISSUE BANKING INDUSTRY.
 3 Q THIS INCLUDED YOU.
 4 A THAT INCLUDED US.
 5 Q AND SO THEN THEY CAME OUT IN MARCH TO MID-
 6 APRIL, WROTE DOWN THESE OBSERVATIONS ON THE 483 AND DO-
 7 YOU UNDERSTAND THAT YOU WERE SUPPOSED TO CORRECT THEIR
 8 OBSERVATIONS BASED UPON THE 483?
 9 A I CERTAINLY HAD A VERY CLEAR UNDERSTANDING
 10 THAT THAT WAS THE EXPECTATION OF THE FDA.
 11 Q AND SO THE OBSERVATIONS LISTED HERE -- AND
 12 I'LL JUST BRIEFLY SYNOPSIS THEM, AND IF YOU -- YOU CAN
 13 FOLLOW ME, CORRECT ME IF I'M WRONG, BUT OBSERVATION ONE
 14 SAYS YOU HAVE A PROCESS WHOSE RESULTS CANNOT BE FULLY
 15 VERIFIED BY SUBSEQUENT INSPECTION AND TEST HAS NOT BEEN
 16 FULLY VALIDATED AND APPROVED ACCORDING TO ESTABLISHED
 17 PROCEDURES. IS THAT RIGHT?
 18 MR. MAJOR: IS THE QUESTION DID YOU READ
 19 IT RIGHT?
 20 BY MR. ALLEN:
 21 Q DID I READ IT RIGHT?
 22 A YES. WHAT IS -- EXCUSE ME, WHAT -- I WAS
 23 TRYING TO FIND OUT WHERE YOU WERE. I KISSED IT, I'M
 24 SORRY.
 25 Q OBSERVATION -- ALL RIGHT, LET ME START

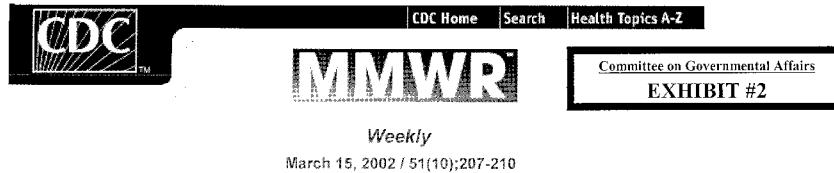
191

1 OVER AGAIN. OBSERVATION ONE SAYS A PROCESS WHOSE
 2 RESULTS CANNOT BE FULLY VERIFIED BY SUBSEQUENT
 3 INSPECTION AND TEST HAS NOT BEEN FULLY VALIDATED AND
 4 APPROVED ACCORDING TO ESTABLISHED PROCEDURES. DID I
 5 READ THAT RIGHT?
 6 A THAT'S WHAT THEY CONTENDED, YES.
 7 Q THEN THEY GO DOWN AND THEY SAY
 8 SPECIFICALLY, AND THEY GIVE YOU A SPECIFIC EXPLANATION
 9 OF THAT. IS THAT CORRECT?
 10 A YES.
 11 Q AND THEN IT SAYS ANNEXATION, IT SAYS UNDER
 12 CONSIDERATION. WHAT DOES THAT MEAN?
 13 A THAT WE WOULD REVIEW -- YOU HAVE A
 14 DISCUSSION WHEN THEY PRESENT THIS, AND YOU GET, IF YOU
 15 DESIRE, THE ABILITY TO MAKE COMMENTS, AND WE SAID --
 16 THERE WAS A GREAT DEAL OF DISCUSSION THAT WE CONTENDED
 17 THAT WE HAD PROPERLY VALIDATED IT. WE HAD A 21-VOLUME
 18 VALIDATION OF THIS SYSTEM THAT WE WERE TOLD BY THE
 19 COMPANY THAT BUILT THE SYSTEM WAS THE MOST THOROUGH THAT
 20 THEY HAD EVER SEEN, AND THE FDA DID NOT ACCEPT IT 'CAUSE
 21 IT DID NOT APPEAR TO DO IT THE WAY ONE WOULD DO IT IN
 22 THE MEDICAL DEVICE INDUSTRY. NONETHELESS, THERE WAS A
 23 FULL VALIDATION IN ACCORDANCE -- IN ACCORDANCE TO THEIR
 24 GUIDANCE DOCUMENT THAT THEY ISSUED ON MARCH 8TH, THE
 25 INVESTIGATORS WERE REQUIRED TO ACCEPT IT AND THEY DID

192

KIMBERLY S. GREENE, CCR.

SC 002464



Update: Allograft-Associated Bacterial Infections --- United States, 2002

Tissue allografts are commonly used in orthopedic surgical procedures; in 1999, approximately 650,000 musculoskeletal allografts were distributed by tissue processors (1). A rare complication of musculoskeletal allografts is bacterial infection (2,3). After the reported death of a recipient of an allograft contaminated with *Clostridium* spp. (an anaerobic spore and toxin-forming organism) (3), CDC investigated this case and solicited additional reports of allograft-associated infections; 26 cases have been identified. This report summarizes the investigation of these cases and describes additional steps given to a tissue processor to enhance tissue transplant safety.

On November 7, 2001, a man aged 23 years underwent reconstructive knee surgery at a hospital in Minnesota using a femoral condyle (bone-cartilage) allograft. On November 10, he developed pain at the surgical site, which rapidly progressed to shock; the patient died the following day (3). Blood cultures obtained premortem grew *Clostridium sordellii*.

On November 13, a man aged 17 years underwent reconstructive knee surgery in Illinois using a femoral condyle (fresh) and a meniscus (frozen). The next day, the patient developed fever, which did not respond to first-generation cephalosporin antibiotics. Eight days after surgery, he was admitted to a local hospital for septic arthritis; his temperature on admission was 103.5° F (39.7° C). The patient received ampicillin-sulbactam, and the fever subsided within 24 hours. The patient is recovering. Cultures for anaerobic bacteria, including *C. sordellii*, were not obtained.

The three allografts received by these two patients came from the same cadaveric donor (donor A) and were supplied by tissue processor A (TP-A). Based on records from the medical examiner, no evidence indicated that donor A was septic or had risk factors for *Clostridium* spp. infection (e.g., injecting drug use or abdominal trauma). The body of donor A was refrigerated 19 hours after death; tissue was procured 23.5 hours after death. One tissue-procurement organization recovered the tissue and sent all tissue to TP-A for processing.

Including the two cases described above, 10 tissues from donor A were transplanted into nine patients located in eight states. No additional infections were identified. CDC obtained 19 nonimplanted tissues from donor A and identified *C. sordellii* in two tissues (fresh femoral condyle and frozen meniscus) and from the fluid bathing the tissues.

TP-A used aseptic processing of harvested tissues. Companion tissue (e.g., a sliver of cartilage from a femoral condyle) was processed alongside the allograft. After suspension of the allograft and companion tissue in an antibiotic/antifungal solution, the companion tissue was cultured. The aerobic

and anaerobic cultures of the companion tissues from donor A were reported as negative at TP-A. No other cultures were taken before tissue processing. No swab cultures were taken; all cultures were destructive (i.e., performed on tissue that had been ground up).

To identify additional cases of allograft-associated infections, CDC solicited case reports through electronic listservers and *MMWR* (2,3) and by contacting the Food and Drug Administration (FDA) and state regulatory authorities (2). A case of allograft-associated infection was defined as any surgical site infection (SSI) at the site of allograft implantation occurring within 12 months of allograft implantation in an otherwise healthy patient with no known risk factors for SSI (e.g., diabetes). Cases could be culture-negative if diagnosed by infectious diseases physicians or surgeons and diagnostic (e.g., knee aspirate) or operative findings supported SSI diagnosis. If only *Staphylococcus aureus* or *Staphylococcus* spp. were isolated, patients were excluded unless additional epidemiologic or microbiologic evidence suggested allograft contamination.

As of March 11, 2002, CDC has received 26 reports of bacterial infections associated with musculoskeletal tissue allografts including the previously reported cases (2,3). Thirteen (50%) of the 26 patients were infected with *Clostridium* spp. (*C. septicum* [12], *C. sordellii* [one]); 11 (85%) of these patients received tissue processed by TP-A. Allografts that were implicated in *Clostridium* spp. infections were tendons used for anterior cruciate ligament (ACL) reconstruction (eight), femoral condyles (two), bone (two), and meniscus (one). Eleven (85%) of the allografts were frozen and two (15%) were fresh (femoral condyles). All allografts were processed aseptically but did not undergo terminal sterilization. In 11 of these 13 cases, additional evidence (e.g., common donors or cultures of nonimplanted tissue) implicated the allograft as the source of the infection. CDC has requested additional information for the other two cases. The median age of these 13 patients was 35 years (range: 15–52 years); onset of symptoms occurred at a median of 8.5 days (range: 2–85 days) following allograft implantation. One patient died.

Eleven patients were infected with gram-negative bacilli; five had polymicrobial infection. Cultures from two patients were negative: the Illinois patient and a patient with necrotizing soft tissue infection treated with multiple debridements, hyperbaric oxygen, and intravenous antibiotics that covered anaerobes. The transplanted tissues included ACL (10), femoral condyle (one), meniscus (one), and bone (one). One tissue was fresh (femoral condyle), one was freeze dried (bone), and the rest were frozen. For eight (62%) of these 13 cases, additional evidence implicated the allograft (e.g., common donors or positive pre-implantation or processing cultures with matching microorganisms) (2). CDC continues to investigate these cases. Eight patients received allografts that had undergone aseptic processing but no terminal sterilization. Three patients received allografts that were reported to have undergone gamma irradiation.

In response to the initial case investigation and the subsequent reports of *Clostridium* spp. infections, CDC provided to TP-A some additional steps to reduce the risk for allograft associated infections.

When possible, a method that can kill bacterial spores should be used to process tissue. Existing sterilization technologies used for tissue allografts such as gamma irradiation, or new technologies effective against bacterial spores should be considered. Unless a sporicidal method is used, aseptically processed tissue should not be considered sterile, and health-care providers should be informed of the possible risk for bacterial infection.

If no sporicidal method is available (e.g., for certain tissues such as fresh femoral condyles), efforts should be made to minimize the potential for *Clostridium* spp. and other bacterial contamination. First, tissue should be cultured before suspension in antimicrobial solutions (4), and if *Clostridium* spp. or other bowel flora are isolated, all tissue from that donor that cannot be sterilized should be

discarded. Second, culture methods should be validated to ensure that residual antimicrobials do not result in false negative culture results (5). Performing both destructive and swab cultures should be considered. Third, recommended time limits for tissue retrieval should be followed (4).

After receiving a report of potential allograft-associated infection, remaining tissue from that donor should not be released until it is determined that the allograft is not the source of infection (4). Tissue processors should contact health-care providers of recipients of tissue from the same donor implicated in an allograft-associated infection. In these cases, a sample of nonimplanted tissues that underwent the same processing method should be cultured by an independent laboratory using a validated method. CDC has recommended that TP-A perform a one-time audit of its unreleased tissue inventory to estimate the proportion of unreleased tissue that might be contaminated with microorganisms or spores.

Reported by: LK Archibald MD, DB Jernigan MD, Div of Healthcare Quality Promotion, National Center for Infectious Diseases; MA Kainer, MD, EIS Officer, CDC.

Editorial Note:

Tissue allografts can improve substantially the quality of life for many patients. However, infections associated with bacterial contamination of allografts can result in serious morbidity and death (2,3). As of March 11, 26 patients with allograft-associated infections have been identified: 13 with *Clostridium* spp. infection and 14 associated with a single tissue processor. The findings in this report have important implications for patient safety and indicate that current federal regulations and industry standards on processing and quality control methods need to be enhanced and implemented to prevent *Clostridium* spp. and other allograft-associated infections.

At CDC, destructive cultures of nonimplanted tissues from donor A were positive for *C. sordellii*. In contrast, destructive cultures of the companion tissue from donor A were reported to be negative at TP-A. Two factors might explain this discrepancy. First, because tissues were cultured at TP-A only after suspension in the antibiotic/antifungal solution, residual antibiotics on the tissues might have caused a false-negative culture result because of bacteriostasis. Second, cultures of the smaller companion tissues might not have been representative of the allografts. Although American Association of Tissue Banks standards recommend that cultures be obtained before and after processing, these standards do not address the potential problem of bacteriostasis after processing or specify a culture method (4). Although destructive cultures used by TP-A are very sensitive, a combination of swab and destructive cultures would be most sensitive in detecting bacterial contamination (6).

Donor A tissue probably became hematogenously seeded by bowel flora, including *Clostridium* spp., before harvesting (7). Factors that may contribute to contamination with bowel flora include time interval between death and tissue retrieval and delays in refrigeration and mode of death (e.g., trauma) (7). Aseptic processing does not eradicate contamination with organisms (2), and antibiotic/antifungal solutions will not eliminate spores of organisms such as *Clostridium* spp.

Sterilization of tissue that does not adversely affect the functioning of tissue when transplanted into patients is the best way to reduce the risk for allograft-associated infections. However, two sterilization methods (ethylene oxide and gamma irradiation) that would eliminate spores have associated technical problems that limit their use in processing of tissues for transplantation (2). New low-temperature chemical sterilization technologies that kill spores (8) but preserve the biomechanical integrity and function of some allografts are being evaluated (9,10).

FDA regulations state that each tissue bank is required to have written procedures for prevention of infectious disease contamination or cross-contamination by tissue during processing. In response to these cases reports, FDA has released new guidelines for tissue processors (<http://www.fda.gov/cber/guidelines.htm#tissval>).

CDC, in collaboration with state health departments, tissue processors, and clinicians, continues to solicit and investigate case reports to identify risk factors associated with acquisition of infection following receipt of an allograft. When septic arthritis occurs after use of an allograft, contamination should be suspected, and diagnostic work-up should include obtaining anaerobic cultures. Clinicians should consider expanding empiric antibiotic therapy to include agents effective against gram-negative organisms and anaerobes. Clinicians should report infections involving allograft tissue to tissue processors, FDA's Medwatch System, and CDC, telephone (800) 893-0485.

Acknowledgements

This report is based on data contributed by JC Davis, MD, Alabama Sportsmedicine and Orthopedic Center, Birmingham, Alabama; SA Barbour, MD, Warren King Sports Medicine Fellowship; W King, MD, Palo Alto Medical Foundation, Palo Alto, California; J Rosenberg, MD, Div of Communicable Disease Control, California Dept of Health Svcs; DC Bartley, MD, St Vincents Medical Center, Jacksonville; D Dodson, MD, West Palm Beach; JM Malecki, MD, Palm Beach County Health Dept; AC Morse, Div of Sports Medicine, Florida Orthopedic Institute, Tampa; OV Martinez, PhD, Univ of Miami, Miami; S Wiersma, MD, Florida Dept of Health; HJ Cohen, MD, Northside Hospital; G Cierney III, MD, St Joseph's Hospital; MA Blass, MD, Georgia Infectious Diseases; EW Carson, MD, Resurgens Orthopaedics; DL Dickensheets, MD, JC Garrett, MD, Atlanta, Georgia; DJ Raab, MD, Illinois Bone and Joint Institute, Des Plaines; MJ Joyce, MD, American Academy of Orthopaedic Surgeons, Rosemont, Illinois; T Tibbot, Indiana Cardiac Retrieval, New Haven, Indiana; B Lutz, MD, Memorial Medical Center-Baptist Campus, New Orleans; R Ratard, MD, Louisiana Dept of Health and Hospitals; BS Wolock MD, Orthopedic Associates, Towson office, Baltimore; RJ Brechner, MD, Maryland Dept of Health and Mental Hygiene; SM Mulawka, MD, DJ Whitlock, MD, SJ Petrowski, MF Buhl, St. Cloud Hospital, St Cloud; PM Hoeft, MD, Rice Memorial Hospital, Willmar; KH LeDell, MPH, R Lynfield, MD, RN Danila, PhD, HF Hull, MD, Minnesota Dept of Health; EA Bresnitz, MD, New Jersey Dept of Health and Senior Svcs; SG Jenkins, PhD, Mt Sinai Medical Center, New York; J Linden, MD, Blood and Tissue Resources, New York State Dept of Health; D Perrotta, PhD, Texas Dept of Health; DA Deneka, MD, Middle Tennessee Orthopedics and Sports Medicine, Murfreesboro; TF Jones, MD, AS Craig, MD, Tennessee Dept of Health; J Mowe, SH Doppelt, MD, RE Stevenson, PhD, American Association of Tissue Banks, McLean, Virginia; RD Noyce, MD, Midelfort Clinic, Eau Claire; TA Israel, MD, Sports Medicine, Luther/Midelfort, Mayo Health Systems, Eau Claire; JP Davis, MD, Wisconsin Div of Public Health; BJ Jensen, MS, MJ Arduino, DrPH, DN Whaley, HT Holmes, PhD, Div of Healthcare Quality Promotion, National Center for Infectious Diseases; DL Kirschke MD, ML Castor MD, EIS officers, CDC.

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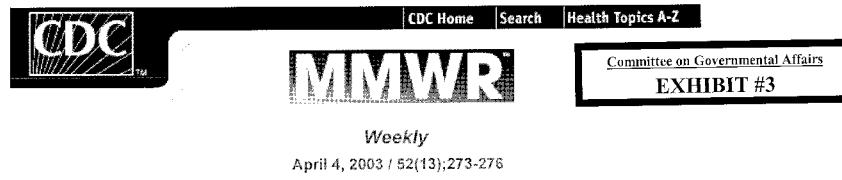
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Hepatitis C Virus Transmission from an Antibody-Negative Organ and Tissue Donor --- United States, 2000--2002

In June 2002, a physician reported to the Oregon Department of Human Services (DHS) a case of acute hepatitis C in a patient who had received a patellar tendon with bone allograft from a donor approximately 6 weeks before onset of illness. At the time of the donor's death in October 2000, his serum had no detectable antibody to hepatitis C virus (anti-HCV). The ensuing investigation conducted by CDC and DHS confirmed that the donor, although anti-HCV--negative, was HCV RNA--positive and the probable source of HCV infection for at least eight organ and tissue recipients. This report summarizes the preliminary results of the investigation. Although transmission from anti-HCV--negative tissue donors probably is rare, determining the frequency of transplantsations from such donors and the risk for transmitting HCV to recipients is important in evaluating whether additional prevention measures are warranted.

The donor was a man in his 40s with a history of hypertension and heavy alcohol use who died of an intracranial hemorrhage. At the time of death, he had no signs or symptoms of hepatitis, and his alanine aminotransferase and aspartate aminotransferase levels were normal. Physical examination revealed no skin markings indicative of injection-drug use or evidence of liver disease. A questionnaire administered to the donor's next of kin revealed no history of injection-drug use or blood transfusion.

At the time of the donor's death, his serum tested negative for anti-HCV by a second-generation enzyme immunoassay (EIA) (Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois) and negative for human immunodeficiency virus (HIV)-1, HIV-2, human T-lymphotropic virus (HTLV) I, HTLV II, hepatitis B virus, and syphilis. In July 2002, stored, frozen serum obtained premortem from the donor tested negative for anti-HCV with a third-generation EIA (ORTHO® HCV Version 3.0 ELISA, Ortho-Clinical Diagnostics, Raritan, New Jersey) but positive for HCV RNA (AMPLICOR® HCV Test, version 2.0, Roche Molecular Systems, Branchburg, New Jersey). The donor's HCV genotype was 1a, as determined from the 300-nucleotide sequence of the nonstructural coding region NS5b (1,2).

A case was defined as laboratory-confirmed HCV infection, with a viral genotype identical to that of the donor, in a recipient not known to have been infected before transplantation. A definite case was defined as one that occurred in a recipient who was both anti-HCV-- and HCV RNA--negative before transplantation. A probable case was defined as one that occurred in a recipient for whom no serum was available before transplantation.

The organ procurement and tissue distribution agencies provided an inventory of grafts recovered from the donor and the contact information for each health-care provider or facility that had received grafts. Health-care providers were contacted to obtain clinical information and to arrange for testing of recipients. Recipients' post-transplantation and stored pretransplantation sera, when available, were tested for anti-HCV by EIA 2.0 or 3.0 and for HCV RNA (by using either AMPLICOR® HCV Test, version 2.0, or HCV RNA DetectRT™ PLUS by TMA, Specialty Laboratories, Santa Monica, California). Specimens positive for anti-HCV by EIA were tested with a supplemental recombinant immunoblot assay (RIBA®, Chiron Corporation, Emeryville, California). HCV genotype was determined for all HCV RNA--positive samples (1,2).

Of 91 organs and tissues recovered from the donor, 44 were transplanted into 40 recipients during October 2000–July 2002. Of the remaining 47 grafts, 44 tissues were removed from distribution in July 2002, and two tissues and one organ had been discarded earlier. Of the 40 recipients, six received organs, 32 received tissues, and two received corneas. Recipients were located in 16 states and two foreign countries. All tissues had been treated with surface chemicals or antimicrobials. Bone grafts also underwent gamma irradiation.

Eight cases were identified among the 40 recipients; all cases were HCV genotype 1a. Among the six organ recipients, post-transplantation serum was available for three, and definite cases occurred in all three. Of the 32 tissue recipients, three were known to have been HCV-infected before transplantation, and test results were not available for another two (one bone and one tendon with bone recipient). Among the remaining 27 tissue recipients, five probable cases occurred: in one of two recipients of saphenous vein, in one of three recipients of tendon, and in all three recipients of tendon with bone (including the index patient). One other recipient was found to be HCV-infected after transplantation with genotype 3a. No cases occurred in recipients of skin ($n = 2$) or irradiated bone ($n = 16$). Of the two cornea recipients, one was infected before transplantation. The other recipient was anti-HCV--negative; however, as of March 27, HCV RNA testing had not been performed.

Reported by: PR Cieslak, MD, K Hedberg, MD, AR Thomas, MD, MA Kohn, MD, Oregon Dept of Human Svcs. F Chai, PhD, OV Nainan, PhD, IT Williams, PhD, BP Bell, MD, Div of Viral Hepatitis, National Center for Infectious Diseases; BD Tugwell, MD, PR Patel, MD, EIS officers, CDC.

Editorial Note:

This report describes transmission of HCV by tissues and organs from a donor whose serum tested anti-HCV--negative at the time of death. However, stored serum tested subsequently was HCV RNA--positive. The donor was the probable source of HCV infection for at least eight recipients of organs or tissues. All cases occurred in recipients of organs or soft tissues; no infections were found among those who had received skin or irradiated bone.

HCV transmission from tissue donors has been reported infrequently; the only tissue types reported previously to transmit HCV are nonirradiated bone and tendon with bone (3–5). By contrast, transplanted organs from infected donors are known to carry a high risk for transmitting HCV (6).

At the time of death, the donor probably was in the 8–10 week window period between infection with HCV and development of a detectable HCV-antibody response (7). Although available data are limited, HCV transmission by organ and tissue donors during this period appears to be uncommon; only one previous report describes HCV transmission from a tissue donor in whom anti-HCV testing (using a less sensitive first-generation assay) was negative (3). The frequency of transplantation from

antibody-negative, HCV RNA--positive organ and tissue donors is not known. However, among voluntary blood donors, whose characteristics probably differ from those of organ and tissue donors, approximately four per 1,000,000 blood donations are from donors who are anti-HCV--negative and HCV RNA--positive (8).

Donor screening is the primary means of preventing transmission of viral infections from organs and tissues. The Food and Drug Administration (FDA) and the Health Resources and Services Administration (HRSA) provide regulatory guidance or oversight for screening of tissue and organ donors. In addition, organ procurement organizations are required by the Centers for Medicare & Medicaid Services to ensure that appropriate donor screening tests are performed by a laboratory certified in accordance with the Clinical Laboratory Improvement Amendments of 1988. The donor screening process includes medical chart review, interview of the donor's next of kin, physical assessment, and testing of donor serum. Guidelines require that organ and tissue donors be tested for anti-HCV.

Nucleic acid testing (NAT) to detect HCV RNA among organ and tissue donors is not performed routinely and has several limitations. Organ viability declines rapidly as a function of time after donor death. Because NAT often is not immediately accessible and can require 1–2 days to complete, it might be impractical in the setting of organ transplantation. By contrast, tissues often can be stored for months to years before use, allowing ample time for NAT. However, postmortem serum frequently is the only sample available for testing from tissue donors. NAT to detect HCV RNA has not been approved by FDA for use on serum samples obtained postmortem, and the performance of available assays in this setting has not been evaluated.

Tissue processing methods (e.g., gamma irradiation) might affect the likelihood of transmission of HCV and other viruses from infected donors (3,9). In this investigation, no cases occurred in recipients of irradiated bone. Irradiation is not applied routinely to all tissue types because it can impair tissue structural integrity.

This investigation was initiated by a clinician who suspected allograft-associated HCV transmission and alerted the state health department. When a new case of hepatitis C is diagnosed in a recent tissue or organ recipient, health-care providers should notify local or state health departments promptly so an investigation can be initiated and, if necessary, tissues can be recalled to prevent further transmission. Centers performing transplantation should maintain adequate records of graft recipients to facilitate investigations of allograft-associated infections.

CDC, in collaboration with FDA and HRSA, will determine whether changes in organ and tissue donor screening guidelines are warranted. Assessing the performance of available NAT and anti-HCV assays in postmortem specimens would provide essential information about the period during which donor screening can be performed reliably. Although transmission from anti-HCV--negative tissue donors probably is rare, determining the frequency of transplantsations from such donors and the risk for transmitting HCV to recipients will be useful for evaluating the benefits and limitations of additional prevention measures.

Acknowledgments

This report is based on information contributed by H Homan, Multnomah County Health Dept; DN Gilbert, MD, Providence Portland Medical Center and Oregon Health and Science Univ; C Corless, MD, Oregon Health and Science Univ; S Kemeny, MD, Providence Portland Medical Center, Portland, Oregon. M Kainer, MD, Tennessee Dept of Health. W Kuhnert, PhD, Div of Viral

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MANNAN S. SISTARE, MINORITY STAFF DIRECTOR AND COUNSEL

United States Senate

COMMITTEE ON
GOVERNMENTAL AFFAIRS
WASHINGTON, DC 20510-6250

12/21/01

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Schwetz:

I am deeply concerned about the recent death of Brian Lykins, the young man in Minnesota who underwent routine knee surgery in which seemingly contaminated cadaveric tissue was used for transplantation. I have long been concerned about the vulnerabilities in the tissue industry and the adequacy of the federal government's oversight. Unfortunately, it appears my concerns are well founded. Not only has one young person lost his life but there have been additional reports of patients who have developed serious infections after receiving donor tissue transplants.

On May 24, 2001, in my capacity as Chairman of the United States Senate's Permanent Subcommittee on Investigations, I held a hearing to evaluate the practices of the tissue industry and the efficacy of the regulatory framework that governs the industry. During the hearing, Dr. Kathryn Zoon, Director of the FDA's Center for Biologics Evaluation and Research, testified that "FDA's goals with regard to human tissue are to: one, prevent the spread of communicable disease; two, to ensure that safety and efficacy is demonstrated for cellular and tissue-based products; and finally, enhance public confidence in these products." Unfortunately, the circumstances surrounding Mr. Lykins' death do not further those goals.

In view of this tragic event, I would like to be advised of the status of the implementation of the agency's tissue action plan, since I am concerned that FDA has not acted as expeditiously as possible to finalize the proposed regulations. For example, the requirement for tissue banks to merely register with the agency took over *three years* to be completed, and I urge you to proceed more aggressively with the remaining components of the plan.

Thank you for your prompt attention to this matter. If you have any questions regarding this matter, please contact Claire Barnard of my staff, at 202-224-5571.

Sincerely,

Susan Collins
Susan M. Collins
United States Senator

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Committee on Governmental Affairs
EXHIBIT #5

United States Senate

COMMITTEE ON
 GOVERNMENTAL AFFAIRS
 WASHINGTON, DC 20510-6250

February 11, 2002

Bernard A. Schwetz, D.V.M., Ph.D.
 Acting Principal Deputy Commissioner
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, Maryland 20857

Dear Dr. Schwetz:

In December 2001, I wrote a letter to the Food and Drug Administration (FDA) inquiring about the status of the agency's long-delayed proposed rules that govern the regulation of human tissue. As you are aware, in February 1997, FDA published its Proposed Approach to the Regulation of Cellular and Tissue-based Products. In March 1998, the agency published the Tissue Action Plan, which included three proposed rules for the regulation of human tissue. Those rules consist of: 1) a requirement for tissue establishments to register and identify product listing; 2) donor suitability determinations; and 3) good tissue practices. I have subsequently learned that since 1998, the only rule which has been finalized is the registration requirement, and that took *three years* to be completed.

I have long been concerned about the vulnerabilities that exist in the tissue industry and the adequacy of the government's oversight. Unfortunately, my concerns have proven well founded. In November 2001, a twenty-three year old man died after undergoing routine knee surgery in which contaminated cadaveric tissue was used for transplantation. As Chairman of the United States Senate's Permanent Subcommittee on Investigations, in May 2001, I held a congressional hearing that examined the efficacy of the regulatory framework. At that time, I concluded that there were some serious gaps in the safety net of regulation but that the proposed rules would be an improvement.

I do not understand why the FDA is taking such an inordinate amount of time to implement the tissue action plan that was first proposed five years ago. Therefore, I would like to have the following questions answered:

- (1) What is FDA's projected date of finalization for the remaining two rules?
- (2) Has FDA established a prescribed cycle of inspections for tissue banks?
- (3) Last year, FDA conducted 132 inspections of tissue banks. How many of those were initial inspections?

-2-

- (4) As of January 2002, 445 tissue banks have registered with FDA. How many of those have been inspected?
- (5) In 2001, how many tissue banks were found to be deficient in some of their practices, and how many were the subject of warning letters or were ordered to take corrective actions steps, including Official Action Indicated or Voluntary Action Indicated?
- (6) What actions has FDA taken against tissue banks that have already received warning letters pursuant to inspections?

Your prompt attention to this matter is appreciated. If you have any questions, please contact Claire Barnard of my staff at 202-224-5571. Thank you.

Sincerely,

Susan Collins
Susan M. Collins
Ranking Minority Member
Permanent Subcommittee on Investigations



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 3 2002

Committee on Governmental Affairs
EXHIBIT #6

The Honorable Susan M. Collins
 Ranking Minority Member
 Permanent Subcommittee on Investigations
 Committee on Governmental Affairs
 United States Senate
 Washington, D.C. 20510-6250

Dear Senator Collins:

Thank you for the letter of February 11, 2002, regarding the status of the implementation of the Food and Drug Administration's (FDA or the Agency) tissue action plan and concerns related to oversight of the tissue industry. The Agency shares your concerns and takes the implementation of the tissue action plan very seriously.

Your questions are restated below in bold, followed by the Agency's response.

Q1. What is FDA's projected date of finalization for the remaining two rules?

As stated in our response to your December 12, 2001 inquiry, the Agency is in the process of drafting final rules based on comments received on the following proposed rules: "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement" and "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." At this time, we do not have a date for the publication and implementation of these final rules. Please also note that as stated in the January 2001 "Report on Oversight of Tissue Banking," by the Office of Inspector General, for the Department of Health and Human Services, oversight of tissue banking is an unfunded mandate for the Agency.

Q2. Has FDA established a prescribed cycle for inspections for tissue banks?

FDA intends to conduct inspections biennially for tissue establishments similar to what exists for blood establishments. However, depending on the availability of resources and a firm's history of compliance, the inspection cycle may have to be adjusted accordingly. Our current tissue inspection program uses a risk-based prioritization system for selecting firms for inspection. Three of the key factors considered in scheduling inspections are whether an establishment has ever been inspected by FDA; if inspected, whether the establishment has a violative history of FDA-conducted inspections; and whether the establishment is accredited by a standard-setting organization.

Page 2 – The Honorable Susan M. Collins

Q3. Last year, FDA conducted 132 inspections of tissue banks. How many of those were initial inspections?

Of the 132 inspections conducted in Fiscal Year 2001, 74 were initial inspections.

Q4. As of January 2002, 445 tissue banks have registered with FDA. How many of those have been inspected?

Currently a total of 458 tissue establishments have registered with the Agency out of which a total of 378 registered, as required by the January 19, 2001, final rule entitled, "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing." Approximately 339 of these 378 firms have been inspected at least once. Of the 339 firms, 208 firms were inspected in FY 2000/2001.

In addition to the 378 required registrants, eighty firms voluntarily registered. These voluntary registrants include hematopoietic stem cell and reproductive tissue processors.

Q5. In 2001, how many tissue banks were found to be deficient in some of their practices, and how many were the subject of warning letters or were ordered to take corrective actions steps, including Official Action Indicated or Voluntary Action Indicated?

Of the 132 establishments inspected in 2001, FDA issued Form FDA 483, "Inspectional Observations," to the management of 51 establishments.

Out of these 51 establishments:

- Two establishments were classified "no action indicated"(NAI), as the establishments voluntarily recalled their products;
- 43 were classified "voluntary action indicated" (VAI);
- Five were classified "official action indicated" (OAI);
- Two establishments received untitled letters (One of the two establishments is part of the Five establishments that were classified "OAI" - (Redacted copies of the untitled letters issued to the two establishments are enclosed).

Of the other four firms classified as "OAI", FDA subsequently issued warning letters to three firms and the fourth firm was reclassified as "VAI" upon follow-up inspection. The remaining 81 firms were classified "NAI" out of which three establishments voluntarily conducted recall of tissue products.

Further, the State of Maryland, working in conjunction with FDA's Center for Biologics Evaluation and Research and the FDA Baltimore District Office, suspended Seabrook Lion's Eye Bank's state license as a result of distribution of unsuitable tissue, and other issues.

Page 3 – The Honorable Susan M. Collins

Q.6 What actions has FDA taken against tissue banks that have already received warning letters pursuant to inspections?

Referring to the response in Q5, of the three establishments that received the warning letters in calendar year 2001, one firm stopped processing corneas; the second firm was reclassified "NAI" upon follow-up inspection; and the third firm is the subject of an ongoing investigation.

Thank you again for contacting us concerning this matter. If you have any further questions, please let us know.

Sincerely,



Melinda K. Plaisier
Associate Commissioner
for Legislation

JOSEPH I. LIEBERMAN, CONNECTICUT, CHAIRMAN
 ARTHUR LEVINE, NEW YORK
 ANNE M. KAGAN, CALIFORNIA
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 RICHARD A. HERTLING, MINORITY STAFF DIRECTOR

FRED THOMPSON, I SEE
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 JAMES B. BROWN, KENTUCKY

Committee on Governmental Affairs
EXHIBIT #7

United States Senate

COMMITTEE ON
 GOVERNMENTAL AFFAIRS
 WASHINGTON, DC 20510-6250

April 12, 2002

The Honorable Tommy G. Thompson
 Secretary of Health and Human Services
 Hubert H. Humphrey Building
 200 Independence Avenue, S.W.
 Washington, D.C. 20201

Dear Mr. Secretary:

I am writing to bring to your attention very troubling delays in the implementation of the Food and Drug Administration's (FDA) proposed regulations that will enhance the safety of human tissue processing.

More than five years ago, FDA examined the health issues that tissue transplantation could pose to the public and concluded that the existing regulatory framework was insufficient. Subsequently, the FDA notified the industry that it intended to impose regulatory changes to strengthen oversight of tissue banks and processors.

As a result, in February 1997, FDA published its "Proposed Approach to the Regulation of Cellular and Tissue-Based Products." Yet, five years later, the majority of the regulatory changes are not final, and I was advised recently by FDA officials that the agency cannot even state when the remaining regulations will be implemented. These reasonable and much-needed regulations will help ensure the safety of tissue transplanted into recipients.

In response to evidence about transmission of HIV to recipients of organs and tissue from an infected donor, FDA began regulating human tissue in 1993, by requiring mandatory donor screening, infectious disease testing, and record-keeping requirements. In 1997, the agency learned that imported foreign tissue had tested positive for hepatitis B and revised the regulations so that tissue banks were also required to screen for HIV-1 and -2, and for hepatitis B and C. In 1997, FDA also published the strategy that would be used to modify the regulatory framework. Subsequently, in March 1998, FDA published the Tissue Action Plan, which contained a description of the steps the agency needed to take to implement the regulatory changes. In May 1998, FDA published the "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue Based Products," which required tissue establishments to register with FDA. That regulation was finalized in January 2001.

In September 1999, FDA published the second proposed regulation, the "Suitability Determination for Donors of Human Cellular and Tissue-Based Products," which expands the screening of potential donors by requiring testing of Creutzfeld-Jakob Disease, syphilis, and Human T-lymphotropic viruses. In January 2001, FDA published the third proposed regulation, the "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue Based Products: Inspection and Enforcement," which would impose standards that are akin to good manufacturing practices. Inexplicably, both regulations are still pending and have not been made final.

I have long been concerned about the vulnerabilities that exist in the tissue industry and the adequacy of the government's oversight. In May 2001, as Chair of the U.S. Senate Permanent Subcommittee on Investigations, I held a hearing that examined the efficacy of the current regulatory framework. At that time, I concluded that the serious gaps in the FDA's regulation of tissues posed a threat to public health.

Unfortunately, recent events have proven that my concerns are well founded. In November 2001, a twenty-three year old man died in Minnesota after undergoing routine knee surgery in which tissue allograft that contained a deadly bacteria was used for transplantation. On March 15, 2002, the Centers for Disease Control and Prevention (CDC) released findings that linked bacterial infections in donated human tissue to allografts that had been used for transplants. CDC officials reported in the Morbidity and Mortality Weekly Report that twenty six cases of infection had been identified, and that number could increase since the investigation is still ongoing. The CDC also made recommendations for improving tissue processing and stated that current federal regulations and industry standards need to be enhanced to prevent further infections.

Dr. Kathryn Zoon, Director of FDA's Center for Biologics Evaluation and Research, testified at the Subcommittee's hearing that FDA is committed to establishing a regulatory framework that will ensure the safe use of human tissue for transplantation. Dr. Zoon estimated that the agency would dedicate \$4.35 million in resources in fiscal year 2002 to the regulation of human tissue. She also testified that cost estimates of the implementation of the tissue regulation would be developed as part of the fiscal year 2003 budget. No estimates have yet been provided by FDA or the Department of Health and Human Services. Furthermore, in January 2001, my colleague Senator Richard Durbin sent a letter to FDA requesting a breakdown of costs for implementation of the proposed regulations, and has never received a response. It is impossible for Congress to work with the Administration to provide the necessary resources unless the figures are identified.

Over five years ago, FDA identified a threat to public health and a need to improve regulatory oversight of tissue establishments. Unfortunately, that threat continues to exist. The Department should act promptly to finalize the regulations and dedicate adequate resources to perform thorough regulatory oversight. I urge you to take the steps necessary to do so before there are any more tragic fatalities.

-3-

I would appreciate your attention to this matter and look forward to hearing from you.

Sincerely,



Susan M. Collins
Ranking Minority Member
Permanent Subcommittee on Investigations

SMC/PSI/cb

**Committee on Governmental Affairs
EXHIBIT #8**



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

RECEIVED BY
SENATE PERMANENT
SUBCOMM. ON INVESTIGATIONS

AUG 30 2002

AUG 28 2002

The Honorable Susan M. Collins
Ranking Minority Member
Permanent Subcommittee on Investigations
Committee on Governmental Affairs
United States Senate
Washington, D.C. 20510-6250

Dear Senator Collins:

Thank you for your letter regarding implementation of the Food and Drug Administration's proposed regulations of human cells, tissues, and cellular and tissue-based products (HCT/Ps). I agree that we need to move ahead as quickly as possible to put these regulations into effect.

I understand that FDA has recently responded by letter to you regarding finalization of the proposed rules, entitled, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement" and "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." Drafting of the final rules is underway, based on comments received on the proposed rules. Although we are not able to forecast a specific date, we are giving publication of the final rules high priority, as indicated by their current listing in the Unified Agenda (67 FR 33072), and expect publication to occur within the next 12 months.

FDA is reviewing the resources required to fully implement its final rules on human cells, tissues and cellular and tissue-based products and will carefully weigh this in the context of other agency priorities. FDA's analysis will help it determine how to best balance competing priorities with our FY 2003 budget request. Representatives from FDA and HHS recently met with Senate staff and discussed the nature and extent of work required to accomplish implementation of this final rule.

I share your concerns and appreciate your interest in this issue. Please call me if you have any further thoughts or questions on this matter.

Sincerely,

Tommy G. Thompson

Committee on Governmental Affairs
EXHIBIT #9

Question 82. Submitted
by Senator Collins:

25

areas. FDA has created a new office that oversees tissues as well as cellular and gene therapies. Close coordination with the Office of Blood Research and Review within the Center for Biologics Evaluation and Research (CBER) will help ensure that consistent donor testing is performed on potential blood and tissue donors. For example, development of West Nile Virus screening tests will be used not only for blood donors, but also for human tissue donors. Human organ transplantation is regulated by the Health Resources and Services Administration, with which CBER has close coordination. FDA continues to increase its capacity to inspect human tissue banks to bring inspections on par with blood bank inspections.

Additionally, FDA continues to work with the tissue industry and the Centers for Disease Control and Prevention to provide guidance on procedures to minimize the chance for cross-contamination of tissues with pathogenic organisms during processing. The Agency intends to work with the medical community to enhance the sharing of information concerning potentially contaminated tissues and to provide guidance on the submission of INDs for new cellular and tissue-based products.

Question 81. FDA plays a critical role in protecting individuals participating in clinical trials. What actions do you believe FDA can take to strengthen protections today, and what legislative steps do you believe are necessary in the future?

My examination of the issues relating to Human Subject Protection has allowed me to appreciate the importance of these issues, which are vital to the integrity and validity of clinical research. As Commissioner I will work with you and others in Congress to assess the need for potential changes to the law or regulations in order to better protect those who participate in clinical trials.

Question 82. Dr. McClellan, over five years ago, the Food and Drug Administration (FDA) examined the health issues that tissue transplantation could pose to the public and concluded that the existing regulatory framework was insufficient. Subsequently, FDA notified the industry that it intended to impose regulatory changes to strengthen oversight of tissue banks and processors, through the "Proposed Approach to the Regulation of Cellular and Tissue-Based Products." Yet, five years later, the majority of the regulatory changes are not final, and the Agency cannot even state when the remaining regulations will be implemented.

In August 2002, Secretary Thompson advised me that while the department is giving publication of the final rules high priority, they are not able to forecast a specific date. When do you anticipate the regulations will be finalized?

I agree with you that improving the safety of tissue banks and processing is an urgent priority. FDA is giving publication of the final rules high priority as indicated by the current listing in the Unified Agenda (67 FR 33072) and expects to complete its rulemaking process within the next 12 months. I will work to expedite this process, and will continue to work closely with you and others to help ensure that all tissue banks and production processes meet the new FDA standards.

Question 83. Dr. McClellan, in May 2001, as Chair of the Permanent Subcommittee on Investigations, I held a hearing that examined the efficacy of the current regulatory framework. During the hearing, Dr. Kathryn Zoon, Director of FDA's Center for Biologics Evaluation and Research, testified that FDA is committed to establishing a regulatory framework that will ensure the safe use of human tissue for transplantation. Dr. Zoon estimated that the Agency would dedicate \$4.35 million in resources in fiscal year 2002 to the regulation of human tissue. She also testified that cost estimates of the implementation of the tissue regulation would be developed as part of the fiscal year 2003 budget. No estimates have yet been provided by FDA or the Department of Health and Human Services (HHS). Furthermore, in January 2001, my colleague Senator Durbin sent a letter to FDA requesting a breakdown of costs for implementation of the proposed regulations, and has never received a response.

It is impossible for Congress to provide the necessary resources unless the figures are identified. Would you please provide an estimate of the costs associated with implementing the regulations?

Thank you for your efforts to promote safe tissue transplantation policy. If confirmed, I look forward to working with you to ensuring that all tissue banks and processors provide safe tissue products.

Question 84. Dr. McClellan, in my bill, S. 2531, The Tissue Transplant Safety Act of 2002, I included a provision that would require the Commissioner of FDA and the Director of the Centers for Disease Control and Prevention (CDC) to jointly develop a single reporting mechanism for use in reporting adverse reactions of tissue. I believe there is a need for a centralize reporting system because the CDC does not currently have access to the same information as FDA. In fact, CDC must now rely on information it solicits from FDA and state health departments. A central repository of adverse reaction information would be very useful in order for CDC to perform timely investigations of public health threats.

Committee on Governmental Affairs

EXHIBIT #10

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax: (404) 253-1202		DATES OF INSPECTION 03/25/2002 - 04/12/2002 FDI NUMBER 3001451326
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs		
FIRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd Nw TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/HumanTissue Processor	
CITY, STATE, ZIP CODE, COUNTRY Kennesaw, GA 30144		
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED: <i>The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.</i>		
OBSERVATION 1 A process whose results cannot be fully verified by subsequent inspection and test has not been fully validated and approved according to established procedures. Specifically, The review of the validation studies for the following: Automated Microbial Detection System [aka Bact/ALERT 3D] revealed the following: a. There are no positive and negative controls used with the samples tested for this study. b. Validation work does not support the reduction of culture incubation from 14 days to 7 days. c. There was no growth promotion testing of the Bact/ALERT media bottles and the Anaerobic Blood Agar plates as part of the validation. d. No study data is available to support worse case situation utilizing one inoculated media in the geometric mean of each incubator drawer in a module. Annotation: Under consideration.		
OBSERVATION 2 Sampling plans are not based on valid statistical rationale. Specifically, the 228 sample size used for the final method study to compare culture results of the Bact/ALERT system versus old method NB001 is not based on a valid statistical rationale.		
OBSERVATION 3 There is no documentation of the revalidation of a process conducted in response to changes or process deviations. Specifically, the firm did not re-validate when they changed the Bact/ALERT anaerobic media bottle from regular media to the anaerobic FAN bottle on or about 3/15/02.		
SEE REVERSE OF THIS PAGE	DATE ISSUED 04/12/2002	
FORM FDA-483 (07-95) REPLACES FORM 483-75 INSPECTOR'S SIGNATURE CMB, ZHCB, RQG, JAS		
INSPECTOR'S COMMENTS		
PAGE 1 OF 8 PAGES		



C- 00619

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs		
FIRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd Nw	
CITY, STATE, ZIP CODE, COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/Human Tissue Processor	
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
<p>OBSERVATION 4</p> <p>A validated process was not revalidated when changes or process deviations occurred.</p> <p>Specifically,</p> <p>1. The TPL autoclave was not re-validated after a sterilization time change on 4/26/01. Additionally, at least 23 cycles failed between 9/23-30/01 and at least 29 cycles failed between 10/24-31/01.</p> <p>2. The packaging validation for the Aline Heat Sealer (E1260C) is not representative of the current operating parameters. The sealer has not been validated to operate at a processing temperature of 310 degrees. At least three complaints of failed seal integrity were noted in the complaint files.</p> <p><i>Annotation: Promised to correct.</i></p>		
<p>OBSERVATION 5</p> <p>Incoming product was not adequately inspected or tested to verify conformance to specifications.</p> <p>Specifically, the firm has not performed a yearly growth promotion test utilizing all the challenge organisms shown on the certificates of conformances for their aerobic and anaerobic media. Firm routinely only uses two or three selected organisms for growth promotion testing on new lots of media that is received.</p>		
<p>OBSERVATION 6</p> <p>Process validation activities and results have not been fully documented.</p> <p>Specifically,</p> <p>1. a) The Anti-Microbial Cocktail Comparison Study lacks documentation of review of all data to support acceptance of the study. Information on study conditions was not documented and several sample processing records (i.e., cardiac tissue samples 461516 and 43609) were not available. b) The study also failed to show data to support the firm's established specification of 22-30 hours treatment of heart valves in the Anti-Microbial Cocktail. None of the samples in the study were processed and evaluated at the lower limit of 22 hours and none were evaluated after 30 hours of treatment.</p>		
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FORM FDA 453 (27-95) PREVIOUS EDITION OBSOLETE		INSPECTORAL OBSERVATIONS PAGE 2 OF 8 PAGES

C- 00620

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		DATE OF INSPECTION 03/25/2002 - 04/12/2002 FEI NUMBER 3001451326
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax: (404) 253-1202	NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs	
FROM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd NW	
GTY, STATE, ZIP CODE, COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/Human Tissue Processor	
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
2. The Biological Safety Cabinet E1241H; NuAire Biological Safety Cabinet, E1241F; Forma Scientific Laminar Flow Hood, E0029M revealed there is no test data under dynamic or full operational conditions to assure the air flow functions as needed for aseptic processing conditions during tissue dissections and during tissue packaging/labeling operations.		
OBSERVATION 7 During production, component and device characteristics are not fully monitored and controlled. Specifically, the bioburden level or microbial load on heart valves is not monitored or evaluated prior to exposure to antibiotic treatment.		
OBSERVATION 8 Requirements have not been established to address the employees' clothing. Specifically, the following observation was made while viewing production operations on 3/26/02: a) Employees are allowed to clean the inside walls and work surface of the biosafety hoods wearing short sleeve surgical scrubs with bare arms exposed during the cleaning.		
<i>Annotation: Promised to correct within 30 days.</i>		
OBSERVATION 9 Employees have not been adequately trained. Specifically, the circulator responsible for disinfecting the Laminar flow hood in the packaging and labeling room on 3/26/02 was observed on using a "W" shaped pattern across the back of the hood instead of an "overlapping" pattern during cleaning. <i>Annotation: Promised to correct within 30 days.</i>		
SEE REVERSE OF THIS PAGE <i>WM, HCB, G, PAB</i>	DATE ISSUED 04/12/2002	
FORM FDA 483 (7/95) PREVIOUS EDITION OBSOLETE	INSPECTORAL OBSERVATIONS	PAGE 3 OF 8 PAGES

C- 00621

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202	DATE OF INSPECTION 03/25/2002 - 04/12/2002 FB NUMBER 3001451326	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs		
FRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd NW	
CITY/STATE ZIP CODE/COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/Human Tissue Processor	
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
<p>OBSERVATION 10</p> <p>Procedures have not been followed to prevent contamination of equipment or product by certain substances.</p> <p>Specifically, the following observation was noted while observing production operations on 3/26/02:</p> <p>1) Blue polylined drapes used to prepare the sterile dissecting field were placed overlapping each other on the working surface. The drapes extending forward and completely covering a major section of the perforated front grill. This perforated front grill is for the uniform downflow of air out of the cabinet and room air inflow.</p> <p>2) Surgical loops used by dissection technicians are stored in wooden boxes that are placed on a cart and other supplies and rolled into the dissection room.</p> <p><i>Annotation: Promised to correct within 30 days.</i></p>		
<p>OBSERVATION 11</p> <p>Failure to prepare, validate, and follow written procedures for prevention of infectious disease contamination and cross-contamination during processing.</p> <p>Specifically, The following observations pertain to our review and assessment of operations as they relate to the processing of Human Tissue for Transplantation.</p> <p>A. There were no evaluations conducted which included bacteriostasis and/or fungistasis testing with the current antibiotic/antifungal cocktail(s) there is no data to ensure they do not interfere with or inhibit organism growth in culture media(s) during Post Processing microbiology QA testing, thereby yielding possible false-negative results.</p> <p>B. Failure to have documentation available for review to ensure that adequate validation studies were conducted which would assist in establishing a consistency of operations in that:</p> <ol style="list-style-type: none"> 1. Incoming tissues are not tested prior to being processed, and there are no current studies showing the firm has knowledge of the average bioburden of tissues received from suppliers. 2. Lack of documentation showing that the residual amount of antibiotics remaining on tissues after treatment with the antibiotic/antifungal cocktail has been determined. 3. Lack of documentation validating that the sample sizes (approximately 0.5-1cm³) obtained for Post Processing microbiology QA testing are adequate and representative of the tissue(s) being processed. <p>C. Records/documentation review of some of the Complaints (Fungus, Bacterial Contamination, General Contamination and Degradation) revealed the following:</p>		
SEE REVERSE OF THIS PAGE	<i>AB, HER, QPQ</i>	DATE ISSUED 04/12/2002
FORM FDA 483 (7/96) PREVIOUS EDITION OBSOLETE		INSPECTORAL OBSERVATIONS PAGE 4 OF 4 PAGES

C- 00622

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION																			
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202		DATE OF INSPECTION 03/25/2002 - 04/12/2002 FD NUMBER 3001451326																	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs																			
FIRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd Nw																		
CITY, STATE, ZIP CODE, COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/HumanTissue Processor																		
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:																			
<p>1. A review of some complaints as bacterial contamination revealed Clostridium, Necrotized Tissue and/or Gram Positive Bacillus/Rod. This review revealed that the firm has received at least 13 complaints dating back to 1998 that involved Clostridium species, Necrotized Tissue and/or Gram Positive Bacillus/Rod. This record review disclosed the following:</p> <ul style="list-style-type: none"> a) Complaint #01-5210123 was reported to the firm on 11/29/01 and Complaint #01-5210124 was reported to the firm on 11/28/01. The review revealed that the tissue allografts (T030) implanted to both recipients were from the same donor (53672). The firm's Microbiology Laboratory isolated microorganisms from tissue samples from donor 53672 prior to the shipment and implantation of the allograft tissues in complaints 01-5210123 and complaints 01-5210124. A total of ten allografts were shipped and/or implanted after the micro laboratory reported the positive microbiological test results. The test results were as follows: <table border="1"> <thead> <tr> <th>DATE TESTED</th> <th>ORGANISM ID</th> <th>DONOR</th> <th>DISPOSITION</th> </tr> </thead> <tbody> <tr> <td>2/5/01</td> <td>C. Paraputrefaction</td> <td>53672</td> <td>Destroyed</td> </tr> <tr> <td>2/8/01</td> <td>C. Septicum</td> <td>53672</td> <td>Destroyed</td> </tr> <tr> <td>3/8/01</td> <td>*Microorganism</td> <td>53672</td> <td>Destroyed</td> </tr> </tbody> </table> <p>*The laboratory failed to identify the genus and species of the microorganism.</p> <ul style="list-style-type: none"> b) Complaint #2001-0090 was reported to the firm on 5/7/01 and Complaint #02-5210189 was reported to the firm on 2/18/02. This review revealed that the tissue allografts (T030) implanted to both recipients were from the same donor (54368). This record review disclosed that the firm shipped at least four (4) tissue allografts from donor 54368 for shipment and/or implantation after the initial complaint was received. c) Complaint #99 1230 was reported to the firm on 12/13/99. This record review disclosed that the firm's Microbiology Laboratory isolated an anaerobic gram-positive rod (the laboratory failed to identify the genus and species of the microorganism) from a tissue sample from donor 43927 on 9/16/99. This review disclosed that a total of three allografts were shipped and implanted after the micro laboratory reported the positive microbiological test results. d) Complaint #98 1104 was reported to the firm on 4/7/98 and Complaint #98 1125 was reported to the firm on 5/12/98. This review revealed that the tissue allografts (T030) implanted to both recipients were from the same donor (31599). This record review disclosed that the firm shipped at least eight (8) tissue allografts from donor 33599 for shipment and/or implantation after the initial complaint was received. e) Failure to prevent cross-contamination of tissue identified as containing microorganisms. For example, laboratory results from a sample for Donor 61640 showed anaerobic gram-negative rods. The microbiology laboratory did not identify the organism. At least eight human allografts from the donor 				DATE TESTED	ORGANISM ID	DONOR	DISPOSITION	2/5/01	C. Paraputrefaction	53672	Destroyed	2/8/01	C. Septicum	53672	Destroyed	3/8/01	*Microorganism	53672	Destroyed
DATE TESTED	ORGANISM ID	DONOR	DISPOSITION																
2/5/01	C. Paraputrefaction	53672	Destroyed																
2/8/01	C. Septicum	53672	Destroyed																
3/8/01	*Microorganism	53672	Destroyed																
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FORM FDA 483 (8790)	PREVIOUS EDITION COMPLETE	INSPECTORAL OBSERVATIONS	PAGE 5 OF 8 PAGES																

C- 00623

SC 002550

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	
DIRECT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202	DATES OF INSPECTION 03/25/2002 - 04/12/2002 RE NUMBER 3001451326
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs	
FIRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd Nw
CITY, STATE ZIP CODE, COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/Human Tissue Processor
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED: were subsequently distributed and implanted. One of the recipients experienced a post-operative infection Clostridium bifermentans). The remaining tissues are currently under recall.	
D. Records/documentation review of the Anti-Microbial Cocktail Comparison Study Protocol 990426-1 revealed the following: 1) There is a statement in this study that states: "Process cardiac and vascular tissue on high speed and orthopedic tissue on medium speed for 30 seconds." There is no data to support/substantiate the use of the Stomacher for the times and speeds utilized. 2) The protocol states that the cocktail solutions for samples should be treated in warm solution B. There is no explanation of what is meant by "warm". 3) This protocol addresses batching the samples. The SOPs does not address batching samples. E. Records/documentation review of the Final Anti-Microbial Study disclosed the following: 1) There is no data to support/substantiate the use of 30 samples in the comparison study that was performed by R&D. 2) The protocol/study fail to show data to justify the use of the parameters 22 hours and 30 hours for cardiac and orthopedic tissues. This study also failed to show the justification of the use of 8 hours and 12 hours for vascular tissue. 3) Microorganisms were identified in four of the samples (41473, 41528, 46589 and 46540. Three of the four microorganisms were later classified as contaminants. There is no data/study conducted by the firm to support the classification of the organisms as contaminants. 4) The statement in the study that states in part: ****The data obtained from this study indicated that both the amikacin and gentamicin were equally effective in reducing the bioburden on the human allograft tissues, in relation to the netilmicin antibiotic.**** There were no bioburden studies conducted. F. The micro lab utilizes a list of five (5) common environmental contaminants (Bacillus species, Diptheroids, Coagulase Negative Staphylococcus, Filamentous fungi and Micrococcus species). The firm does not have any data to justify/support the use of this list of organisms. G. A review of the Complaint process revealed that Research and Development (R&D) handles a critical part of the investigation/follow-up. This review revealed that R&D does not have a written procedure for conducting the follow-up investigation. The record review disclosed the following inconsistencies: 1) Review of complaint #02-5210217 (donor 47357) revealed this complaint involved the development of Endocarditis in the recipient. This report also states that the allograft was implanted on 3/7/01, the patient developed Endocarditis and an abscess. The allograft was scheduled for explant in March 2002. The final conclusion on the report from R&D was taken directly hospital pathologist report.	
SEE REVERSE OF THIS PAGE CWB, THB, LQ, QAB	DATE ISSUED 04/12/2002
FORM FDA 483 (7/98) PREVIOUS EDITION OBSOLETE INSPECTORAL OBSERVATIONS PAGE 6 OF 8 PAGES	

C- 00624

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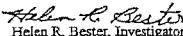
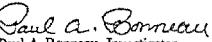
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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		DATES OF INSPECTION
OFFICE ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202		03/25/2002 - 04/12/2002 FIRM NUMBER 3001451326
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Wyk, VP of Quality Assurance/Regulatory Affairs		
FIRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd Nw	
OFFICE, STATE, ZIP CODE & COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/Human Tissue Processor	
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
<p>2) Review of complaint #01-5210090 revealed a specimen was received for testing on 10/5/01. This specimen was mishandled. A memo was written to the file dated 1/16/02, (approximately 3 months later) that attempted to explain the series of events.</p>		
EQUIPMENT <p>H. Records/documentation review of the record for the Stomachers revealed the following:</p> <ol style="list-style-type: none"> 1) The firm failed to perform Installation Qualifications on the Stomachers (E0113F-purchased 10/16/00 and E0113E-date unknown). 2) The firm does not have a maintenance program for the two Stomachers (E0113E and E0113F), Model 80 used in the processing of human tissue. The manufacturer's maintenance manual states in part: "**** It is recommended that the following routine checks be carried out every 6 months unless local regulations or Code of Practice require more frequent service intervals. If the instrument is used very extensively, e.g., double shift working in a laboratory, then the frequency should be increased to monthly intervals. **** The checks that the manual recommends include but is not limited to the following: 1) Functional Check; 2) Electrical Check and 3) Mechanical Check. 		
OBSERVATION 12 <p>Records fail to be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular tissue involved.</p> <p>Specifically, Records/documentation review revealed that the Standard Operating Procedures (SOPs- QS270, QS 2720, QS 2730/ were not followed. This review revealed the following:</p> <ol style="list-style-type: none"> 1) Tissue allografts from Donor #46305, 46308, 46310, 46313, 46315) were under processed for time periods ranging from 39-49 minutes. The firm SOP's states that the minimum time for antibiotic treatment is 22 hours (heart and orthopedic tissue allografts) and 8 hours for vascular tissue allografts. 2) SOP QA-0001 was not followed. The Material Review Board made a decision to approve the tissue allografts for use. **** Material Review Board documentation should be complete and explicit enough to reflect the requirement, the departure from the requirement, the disposition, the rationale for the disposition and the root cause, as necessary, without any further documentation. 3) There were five products (P020, PV00(x2), AV00, and MV10) from the four donors that were released and shipped for implantation 		
SEE REVERSE OF THIS PAGE	<i>Cob, 4/12/02</i>	DATE ISSUED 04/12/2002
FORM FDA 483 (5776) REV. 1/97		PREVIOUS EDITION OBSOLETE
		INSPECTORAL OBSERVATIONS
		PAGE 7 OF 8 PAGES

C- 00625

SC 002552

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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DIRECT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202	DATES OF INSPECTION 03/25/2002 - 04/12/2002	FEI NUMBER 3001451326
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James C. Vander Nyk, VP of Quality Assurance/Regulatory Affairs		
FIRM NAME Cryolife Inc	STREET ADDRESS 1655 Roberts Blvd Nw	
CITY, STATE, ZIP CODE, COUNTRY Kennesaw, GA 30144	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer/HumanTissue Processor	
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
FDA EMPLOYEES' NAMES, TITLES, AND SIGNATURES:		
 Claudette D. Brooks, Investigator	 Helen R. Bester, Investigator	
 Paul A. Bonneau, Investigator	Karen A. Coleman, Investigator	
 Ronnie E. Jackson, Investigator		
SEE REVERSE OF THIS PAGE		DATE ISSUED 04/12/2002
FORM FDA 483 (7/95) PREVIOUS EDITION OBSOLETE		INSPECTIONAL OBSERVATIONS PAGE 1 OF 8 PAGES

C- 00626

SC 002553

Committee on Governmental Affairs
EXHIBIT #11



Biotechnologies for Medicine™

May 15, 2002

Mr. Ballard H. Graham
District Director, HFE-SE160
Food and Drug Administration
60 Eighth Street
Atlanta, GA 30309

Re: Initial reply to Notice of Inspectional Observations (483) from Inspection of 3/25/02-
4/12/02 (FEI # 3001451326).

Dear Mr. Graham:

This submission is in reply to the inspectional observations in the Notice of Inspectional Observations (Notice) issued by investigators C. Brooks, K. Coleman, H. Bester, R. Jackson, and Microbiologist P. Bonneau as a result of the above-cited inspection of CryoLife, Inc., a registered tissue bank (Reg. # FEI 3001451326) and medical device manufacturer (Reg. # 1063481) located at 1655 Roberts Blvd., NW, Kennesaw, GA 30144.

First, I would like to comment on the professional, interactive nature of the inspection. It is clear that the tissue processing industry faces challenges induced by certain sensationalizing of events in the national media. At the outset of this inspection we were informed that the agency's purpose was to investigate two alleged heart valve endocarditis events associated with CryoLife-preserved allograft valves. Under the circumstances, the inspection might have devolved into confusion and acrimony. However, the investigators exhibited willingness and forbearance to discuss the observations, issues, and CryoLife positions openly and thoroughly throughout the inspection. While it is clear that there are some major differences in the positions stated by CryoLife and FDA, as represented by the investigators, CryoLife nonetheless appreciates the consideration extended by the investigators and local district.

CryoLife cooperated fully with this inspection although we noted that these two claims by a single surgeon alleging that heart valves supplied by CryoLife resulted in endocarditis infection in his two patients were isolated cases and there was no pattern of similar complaints and there was no historical basis for assuming a significant public health risk. The valves in question were implanted a significant period of time prior to the onset of symptoms claimed by the reporting surgeon (in the first case the implant was 5 months prior to symptoms and 8 months prior to the complaint; the second was implanted a year prior to the symptoms and complaint). The second complaint had barely been received by CryoLife and we had not yet had the opportunity to initiate our own investigation. In both cases, the investigation conducted by CryoLife revealed, by pathology data submitted by the reporting surgeon's own hospital as well as other review, that the CryoLife-supplied heart valves were not infected. This supported CryoLife's initial hypothesis that the valves were not involved.

1655 Roberts Boulevard, NW • Kennesaw, Georgia 30144
770-419-3355 • 1-800-438-8285 in the USA and Canada • Fax: 770-426-0031

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(CryoLife 483 Response, Cont.)

Thus the regulatory record is clear that as of September 30, 1999 the FDA acknowledged that Part 1270 and 1271 referred directly to testing for HIV and hepatitis and acknowledged that additional, future rulemaking was necessary to expand the scope of 1271 requirements to other infectious diseases. No such regulations have been promulgated to date.

In light of the above regulatory history, there is no legal foundation to support the agency's contention, as asserted in the final Guidance for Industry - Validation of procedures for processing of human tissues intended for Transplantation (Guidance) issued by FDA in March 2002, that infectious diseases include more than HIV or hepatitis under Part 1270.

CryoLife has always agreed that appropriate additional regulation of the tissue banking industry is necessary. Indeed the record shows that CryoLife was instrumental in organizing an effort of all the heart valve processors to propose an outline of Good Tissue Practices for the FDA to consider. However, we object to the current FDA effort to subvert the rulemaking process before a thorough discussion of the effects that such requirements stated in the Guidance will and might have on tissue availability. Many of the observations listed in this 483 are drawn from investigator experience in compliance issues for sterile medical devices. The issues considered within this 483 with regard to tissues are not always directly comparable to such devices.

However, if this Guidance was legitimate, we believe the investigators did not properly apply its directives in certain cases represented in this 483. For example, the Guidance states that the FDA may review a manufacturer's validation data. An observation will be included on the 483 if the manufacturer does not have a validation or does not follow its validated procedures. If the validation is complex or does not appear adequate, the investigator is limited to collecting copies of the records for further FDA evaluation. This appears to be an acknowledgement of the difficulties associated with validating certain processes for tissues and initiates a learning process on the part of the FDA and industry separate from direct enforcement action.

Despite CryoLife's contention that many of the FDA actions, comments, and listed observations are not supported under current regulations, we have attempted to address the issues raised in the 483 response. We believe that certain of the observations raise larger issues that are not resolved technically in the industry, misapply process validation theory from sterile device manufacturing, or are matters of national policy relative to the availability of an adequate supply of human implantable tissue commensurate with reasonable risk. Such issues deserve consideration and we certainly intend to be a constructive part of that dialogue.

If there are further questions or clarifications required, I may be reached at 678.290.4530.

Sincerely,

James C. Vander Wyk
 James C. Vander Wyk, Ph.D.
 Vice-President, Regulatory Affairs and
 Quality Assurance

Committee on Governmental Affairs
EXHIBIT #12

Complaint Record

Cyolife, Inc.
1655 Roberts Blvd, NW
Kennesaw, GA 30144

Document ID: 20010005
Document Date: 03/05/2001
Page: 1

Component Notes													
Customer Contact Log <table border="1" style="width: 100%;"> <thead> <tr> <th>#</th> <th>Date of Contact</th> <th>Notes</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>03/05/2001</td> <td>Acknowledge</td> </tr> <tr> <td>2</td> <td>03/23/2001</td> <td>Joseph Auriemma, Field Assurance spoke to Larry Schumacher, Independent representative concerning patient status. Larry states the patient is doing fine, and was treated with antibiotics.</td> </tr> <tr> <td>3</td> <td>03/30/2001</td> <td>Final letter.</td> </tr> </tbody> </table>		#	Date of Contact	Notes	1	03/05/2001	Acknowledge	2	03/23/2001	Joseph Auriemma, Field Assurance spoke to Larry Schumacher, Independent representative concerning patient status. Larry states the patient is doing fine, and was treated with antibiotics.	3	03/30/2001	Final letter.
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Customer Contact Log Notes													

Complaint Analysis				
Sample(s) Requested On	RGA Number	City Affected	City Returned	Sample(s) Received On
Is this event a complaint? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk		Determined By Joseph Auriemma	Department Field Assurance	Date 03/05/2001
Rationale Incident qualifies as a complaint per definition of complaint in CCP010.				
Is this event FDA reportable? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unk		Determined By Elisa Chi Abruzzo	Department Regulatory Affairs	Date 03/05/2001
Rationale Orthopedic allografts are not classified as medical devices as defined by FDA regulations, and are therefore not reportable.				
Is a foreign report required? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unk		Determined By Elisa Chi Abruzzo	Department Regulatory Affairs	Date 03/05/2001

SC 001221